PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,808,605 Attn: Box Patent Ext.

Inventors: Branca, et al.

Issue Date: February 28, 1989

For: TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
August 5, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith are the following: a) Application for Extension of Patent Term Under 35 U.S.C. §156 with Exhibits (separately bound) and b) Declaration and Power of Attorney for Application for Extension of Patent Term under 35 U.S.C. §156, for U.S. Patent No. 4,808,605. The Application is being submitted in duplicate, and the undersigned certifies that each copy of the attached Application is a duplicate original. In addition, three courtesy copies of all papers filed are being provided for the convenience of the Assistant Commissioner.

DEPOSIT ACCOUNT
NO. 08-2525
OUR ORDER NO. 1068

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

Please charge Deposit Account No. 08-2525 in the amount of $1060.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

A duplicate copy of this cover sheet is enclosed.

Respectfully submitted,

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,808,605

Attn: Box Patent Ext.

Inventors: Branca, et al.

Issue Date: February 28, 1989

For: TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
August [illegible]997

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 35 U.S.C. § 156, Hoffmann-La Roche Inc. ("ROCHE"), a corporation organized under the laws of the State of New Jersey and owner of U.S. Patent No. 4,808,605, by assignment recorded on December 21, 1987 at reel 4809, frames 0515 and 0516, submits this Application for extension of its term.

Applicant seeks extension of the term of U.S. Patent No. 4,808,605 for three (3) years and thirty five (35) days, from November 10, 2007 to December 14, 2010 and certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

The information contained in this document and its Exhibits is provided in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and is listed in the manner set forth in § 1.740.

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product contains mibefradil as the sole active ingredient of the drug Posicor™. Posicor is a selective T-type calcium channel, ion influx inhibitor available as a tablet for oral administration. It is approved to be supplied in tablets, each tablet containing 50 mg or 100 mg mibefradil dihydrochloride, with the following inactive ingredients: lactose anhydrous, corn starch, polyvinyl pyrrolidone, talc, sodium stearyl fumarate, hydroxypropyl methyl cellulose, ethyl cellulose, triacetin and titanium dioxide, with synthetic yellow iron oxide (50 mg tablet) and synthetic red iron oxides (100 mg tablet) (Exhibit 1).

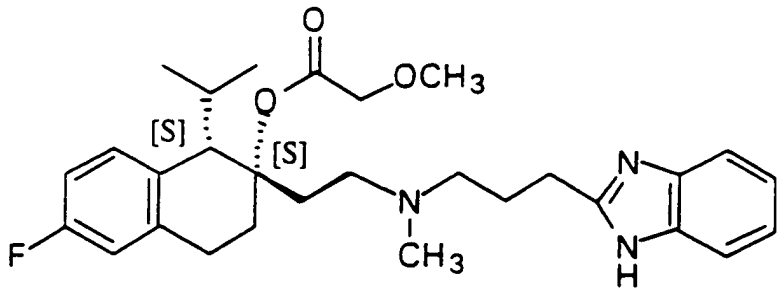
"Mibefradil" is the non-proprietary name approved by the USAN council for the free base of the active ingredient of Posicor.

Mibefradil also has the following chemical names:

1. [1S,2S]-2-[2-[[3-[2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

   (1S-cis)-Methoxyacetic acid 2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino] ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester.

2. Mibefradil has the structural formula:



The term "approved product" is defined in 35 U.S.C. § 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. § 156(f)(1)(A) to comprise a "drug product" which is described in 35 U.S.C. § 156(f) (2) to include "the active ingredient of a new drug, antibiotic drug, or human biological product . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." Accordingly, the approved product subject to this Application includes mibefradil as well as its salts as a single ingredient or in combination with another active ingredient.

(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 301 et seq.

(3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

Posicor was approved by the Food and Drug Administration ("FDA") for commercial marketing or use under Section 505 of the FD&C Act on June 20, 1997 (Exhibit 2).

(4) In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The sole active ingredient in the approved product is mibefradil, which active ingredient has not been previously approved for commercial marketing or use under the FD&C Act, The Public Health Services Act or the Virus-Serum-Toxin Act.

(5) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to § 1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is August 18, 1997 .

(6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of the Inventor, The Patent Number, The Date Of Issue, And The Date of Expiration

The complete identification of the patent for which an extension is being sought is:

Inventors:	Quirico Branca Roland Jaunin Hans P. Märki Fränzi Marti Henri Ramuz
Patent No:	4,808,605
Issue Date:	February 28, 1989
Expiration Date:	November 10, 2007 (without extension)

(7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 4,808,605 is attached as Exhibit 3.

(8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In the Patent

No disclaimer or reexamination certificate has been issued for U.S. Patent No. 4,808,605. A copy of the certificate of correction issued October 17, 1995 and receipt of maintenance fee payment are attached as Exhibit 4.

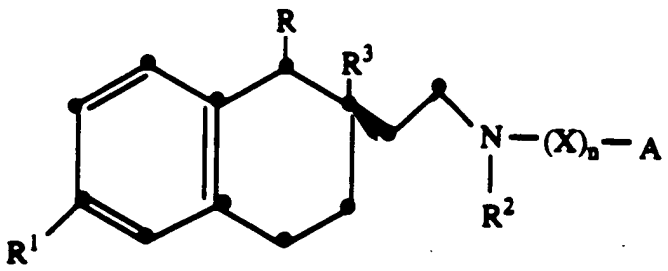
(9) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which Each Applicable Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

United States Patent No. 4,808,605 claims the approved product, mibefradil including its salts, in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 15.

Claim 1 (as corrected by Certificate of Correction) reads as follows:

1. A compound of the formula



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wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1-C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy, lower-alkylaminocarbonyloxy; or arylaminocarbonyloxy or aryl-lower-alkylamino-carbonyloxy, wherein aryl is phenyl or phenyl mono- or multiply-substituted by halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, nitro or amino; X is C_1-C_{18}-alkylene which can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group wherein the substituents are selected from the group consisting of lower alkyl and phenyl; or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo-[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrro[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl wherein the substituents are selected from the group consisting of C_1-C_{12}-alkyl, phenylloweralkyl, halo, morpholinoethyl and pyridylmethyl and wherein the last two of said

heterocycles may be partially hydrogenated; and n is number 0 or 1, in the form of a racemate or an optical antipode, an N-oxide, or a pharmaceutically usable acid addition salt thereof.

Claim 1 reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylene (propylene), A is benzimidazolyl and n is 1.

Claim 2 reads as follows:

2. A compound in accordance with Claim 1, wherein R is isopropyl.

As described above, Claim 1, from which Claim 2 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 2 reads on mibefradil and its salts.

Claim 3 reads as follows:

3. A compound in accordance with Claim 2, wherein R^3 is hydroxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy or lower-alkylaminocarbonyloxy.

As described above, Claim 2, from which Claim 3 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 3 reads on mibefradil and its salts.

Claim 4 reads as follows:

4. A compound in accordance with Claim 3, wherein R^3 is isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy.

As described above, Claim 3, from which Claim 4 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 4 reads on mibefradil and its salts.

Claim 5 reads as follows:

5. A compound in accordance with Claim 1, wherein n is the number 1.

As described above, Claim 1, from which Claim 5 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 5 reads on mibefradil and its salts.

Claim 6 reads as follows:

6. A compound in accordance with Claim 1, wherein R^1 is fluorine.

As described above, Claim 1, from which Claim 6 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 6 reads on mibefradil and its salts.

Claim 7 reads as follows:

7. A compound in accordance with Claim 1, wherein R^2 is methyl.

As described above, Claim 1, from which Claim 7 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 7 reads on mibefradil and its salts.

Claim 8 reads as follows:

8. A compound in accordance with Claim 1, wherein X is C_3-C_7-alkylene.

As described above, Claim 1, from which Claim 8 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 8 reads on mibefradil and its salts.

Claim 9 reads as follows:

9. A compound in accordance with Claim 8, wherein X is propylene, butylene, pentamethylene or hexmethylene.

As described above, Claim 8, from which Claim 9 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 9 reads on mibefradil and its salts.

Claim 10 reads as follows:

10. A compound in accordance with Claim 1, wherein A is 2-benzimidazolyl, 2-benzthiazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydro-pyrrolo[2,1-c] [1,4]benzodiazepine-5,11-dion-10-yl or 1-methyl-4,5-diphenyl-2-imidazolyl.

As described above, Claim 1, from which Claim 10 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl (2-benzimidazolyl) and n is 1. Therefore, Claim 10 reads on mibefradil and its salts.

Claim 11 reads as follows:

11. A compound in accordance with Claim 10, wherein A is 2-benzimidazolyl or 2-benzthiazolyl.

As described above, Claim 10, from which Claim 11 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl (2-benzimidazolyl) and n is 1. Therefore, Claim 11 reads on mibefradil and its salts.

Claim 12 reads as follows:

12. A compound in accordance with Claim 1, wherein R is isopropyl, R^3 is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy, R^1 is fluorine, R^2 is methyl, X is propylene, butylene, pentamethylene or hexamethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

As described above, Claim 1, from which Claim 12 depends, reads on mibefradil and its salts, when, in Claim 1, R is lower-alkyl (isopropyl), R^1 is halogen (fluorine), R^2 is C_1-C_{12}-alkyl (methyl), R^3 is lower-alkoxy-lower-alkyl carbonyloxy (methoxyacetyloxy), X is C_1-C_{18}-alkylamino (propylene), A is benzimidazolyl and n is 1. Therefore, Claim 12 reads on mibefradil and its salts.

Claim 15 reads:

15. A compound in accordance with Claim 1, [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl] methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate.

Mibefradil is [1S,2S]-2-[2-[[3-[2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate, therefore, Claim 15 reads on mibefradil and its salts.

As demonstrated above, Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 15 read on both mibefradil and its salts.

(10) A Statement, Beginning on a New Page, of The Relevant Dates And Information Pursuant To 35 U.S.C. 156(g) In Order To Enable The Secretary Of Health and Human Services or the Secretary of Agriculture, As Appropriate, To Determine the Applicable Regulatory Review Period as Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) or a Product License Application (PLA) Was Initially Submitted And The NDA or PLA Number And The Date On which The NDA Was Approved or the Product License Issued

a)	Effective date of the investigational new drug application (IND) and IND number. (for the treatment of Hypertension and Chronic Stable Angina Pectoris)	July 24, 1992 (Exhibit 5) IND No. 39,901
b)	Date on which a New Drug Application (NDA) was initially submitted and NDA number:	March 8, 1996 (Exhibit 6) NDA No. 20-689
c)	Date on which NDA was approved:	June 20, 1997 (Exhibit 2)

(11) A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of communications involving ROCHE, Marion Merrell Dow Inc. ("MMD") and the FDA during the regulatory review period is attached as Exhibit 7. While the IND was submitted by MMD, it was submitted under terms of an agreement by which ROCHE and MMD collaborated in a joint effort for developing mibefradil as a pharmaceutical product. Under the terms of the agreement, MMD had the sole right and responsibility to take actions in the U.S. consistent with a Global Development Program drafted by the Global Joint Development Committee (of which Roche and MMD were represented) to obtain and maintain registration of mibefradil. By letter dated December 10, 1992, ownership of IND 39,901 was transferred from MMD to ROCHE. This Exhibit 7 lists the date of the communication and a brief summary of the subject matter of the communication. This chronology provides a description of the significant activities undertaken by ROCHE/MMD during the applicable review period. For convenience, the chronology is divided into a Testing Phase and an Application Phase.

If necessary, ROCHE reserves the right to supplement its summary in Exhibit 7 with materials from which it was derived and other evidence related to applicant's conduct in obtaining the approval of POSICOR, See, e.g., 21 C.F.R. § 60.32.

(12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Eligibility

Under the law and in the opinion of Applicant, U.S. Patent No. 4,808,605 is eligible for an extension under 35 U.S.C. § 156.

In particular, 35 U.S.C. § 156(a) in its relevant parts, provide that the term of a patent shall be extended if the following requirements are satisfied: (1) the patent claims a product, a method of using a product or a method of manufacturing a product; (2) the term of the patent has not expired before an application for extension is submitted; (3) the term of the patent has never been extended; (4) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (5) the product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(a) before its commercial marketing or use; and (6) the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 4,808,605 claims a product.

2. The term of U.S. Patent No. 4,808,605 presently will expire on November 10, 2007 and thus, the patent has not expired before submission of this Application.

3. The term of U.S. Patent No. 4,808,605 has never been extended under 35 U.S.C. § 156.

4. This Application is submitted by ROCHE, the owner of record of U.S. Patent No. 4,808,605. This Application is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 within the sixty (60) day period beginning on June 20, 1997 and ending August 18, 1997. The product received permission for marketing or use under FD&C Act. This Application contains the information required under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

5. The product was subject to a regulatory review period under Sections 505 of the FD&C Act before its commercial marketing or use, as evidenced by the chronology (Exhibit 6) and the Letter of Approval from the FDA, dated June 20, 1997 (Exhibit 2).

6. The permission for the commercial marketing or use of mibefradil, after the regulatory review period is the first permitted commercial marketing or use of a product having mibefradil in any form as its active ingredient, under the provisions of the FD&C Act under which such regulatory review period occurred. This is confirmed by the absence of any approved drug application for mibefradil in any form prior to June 20, 1997.

Accordingly, U.S. Patent No. 4,808,605 satisfies the requirements for an extension under 35 U.S.C. § 156.

Length

In the opinion of Applicant, the term of U.S. patent No. 4,808,605 should be extended for a period of three years and thirty five days, from November 10, 2007 to December 14, 2010.

This extension was determined on the following basis:

Testing Phase (37 C.F.R. § 1.775(c) (1))

For the approved product, that portion of the regulatory review period as defined in 35 U.S.C. 156 (g) (1) (B) (i) ("Testing Phase") commenced on July 24, 1992 and ended on March 8, 1996, which is 1,323 days.

Application Phase (37 C.F.R. § 1.775(c) (2))

For the approved product, that portion of the regulatory review period as defined under 35 U.S.C. 156 (g) (1) (B) (ii) ("Application Phase") commenced on March 8, 1996 and ended on June 20, 1997, which is 469 days.

Regulatory Review Period (37 C.F.R. § 1.775(c))

As defined in 35 U.S.C. 156 (g) (1) (B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of 1792 days.

Reduction for Review Prior to the Issue of The Patent (37 C.F.R. § 1.775 (d) (1) (i))

The applicable regulatory review period is reduced by that period of review occurring before and on the date the patent issued.

U.S. Patent No. 4,808,605 (Exhibit 3) issued February 28, 1989 and the IND was filed June 24, 1992 . Accordingly, no reduction for review prior to the issue of the patent applies.

Due Diligence Reduction to Regulatory Review Period (37 C.F.R. § 1.775 (d) (1) (ii))

Under 35 U.S.C. § 156(c) (1), the Testing Phase and Application Phase of the regulatory review period are reduced by the period during which the applicant for the patent extension, in the regulatory review period, did not act with due diligence. In the opinion of the Applicant and illustrated by the summary in Exhibit 6, it acted with due diligence during both periods of time. Thus, there is no reduction in the regulatory review period because of lack of due diligence.

One-Half Testing Phase Reduction (37 C.F.R. § 1.775 (d) (1) (iii))

Under 35 U.S.C. § 156(c) (2), the 1792 day regulatory review period is reduced by one-half of the 1323 day Testing Phase. One-half of the Testing Phase is 662 days. Thus, the 1792 day regulatory review period is reduced by 662 days leaving a final revised regulatory review period of 1130 days.

Fourteen Year Cap (37 C.F.R. § 1.775 (d) (2) - (4)

Under 35 U.S.C. § 156(c) (3) should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceed fourteen (14) years, the period of extension is reduced so that the total of both such periods does not exceed fourteen (14) years. In applying section 156(c) (3), the final revised regulatory review period as calculated above (1130 days) is added onto the end of the original term of the patent November 10, 2007 resulting in a date of December 14, 2010. Alternatively, fourteen (14) years is added to the NDA approval date (June 20, 1997) resulting in a date of June 20, 2011. The earlier of the above two dates, December 14, 2010 is selected.

Two and Five Year Extension Limits (37 C.F.R. § 1.775 (d) (5) & (6)

A patent issued after September 24, 1984 is limited to a maximum extension of five years.

U.S. Patent No. 4,808,605 (Exhibit 3) issued on February 28, 1989. Accordingly, the patent is eligible for an extension of up to five years.

As set forth above, the term of U.S. Patent No. 4,808,605 is eligible for an extension of three (3) years and thirty five (35) days from November 10, 2007 to December 14, 2010.

(13) A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

For completeness, applicant notes that a NDA is pending for mibefradil for treatment of congestive heart failure.

(14) The Prescribed Fee for Receiving and Acting Upon the Application for Extension

Applicant encloses (in duplicate) a transmittal letter requesting the amount of $1060.00 be charged to Account No. 08-2525.

(15) The Name, Address and Telephone Number Of The Person to Whom Inquiries and Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Please direct all telephone calls to:

Ellen Ciambrone Coletti
(937) 235-5171

(16) A Duplicate of These Application Papers, Certified As Such

A certified duplicate is enclosed.

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

(17) An Oath or Declaration As Set Forth In Paragraph (b) of 37 C.F.R. § 1.740

Applicant attaches a declaration as set forth in 37 C.F.R. § 1.740(b), signed by an officer of Roche, the owner of record of U.S. Patent No. 4,808,605, who is authorized to practice before the Patent and Trademark Office and who has general authority to act on ROCHE's behalf in patent matters.

Request for Extension

Having included in this Application all of the requisite information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant requests an extension of U.S. Patent No. 4,808,605 for three (3) years and thirty five (35) days from November 10, 2007 to December 14, 2010, by reason of its claims encompassing mibefradil and its salts as a single entity or in combination with another active ingredient.

Respectfully submitted,

HOFFMANN-LA ROCHE INC.

By: _____

Ellen Ciambrone Coletti
Name (Print)

Senior Counsel
Title

Registration No. 34140 8/5/97
Date

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 U.S.C. § 156 including its exhibits is being submitted as duplicate originals.

By: _____
Ellen Ciambrone Coletti
Senior Counsel
Registration No. 34140

Date: 8/5/97

39259

#12

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,808,605

Attn: Box Patent Ext.

Inventors: Branca, et al.

Issue Date: February 28, 1989

For: TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
August 5, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith are the following: a) Application for Extension of Patent Term Under 35 U.S.C. §156 with Exhibits (separately bound) and b) Declaration and Power of Attorney for Application for Extension of Patent Term under 35 U.S.C. §156, for U.S. Patent No. 4,808,605. The Application is being submitted in duplicate, and the undersigned certifies that each copy of the attached Application is a duplicate original. In addition, three courtesy copies of all papers filed are being provided for the convenience of the Assistant Commissioner.

DEPOSIT ACCOUNT
NO. 08-2525
OUR ORDER NO. 1068

U.S. Patent No. 4,808,605
Issue Date: February 28, 1989

Please charge Deposit Account No. 08-2525 in the amount of $1060.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

A duplicate copy of this cover sheet is enclosed.

Respectfully submitted,

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39258

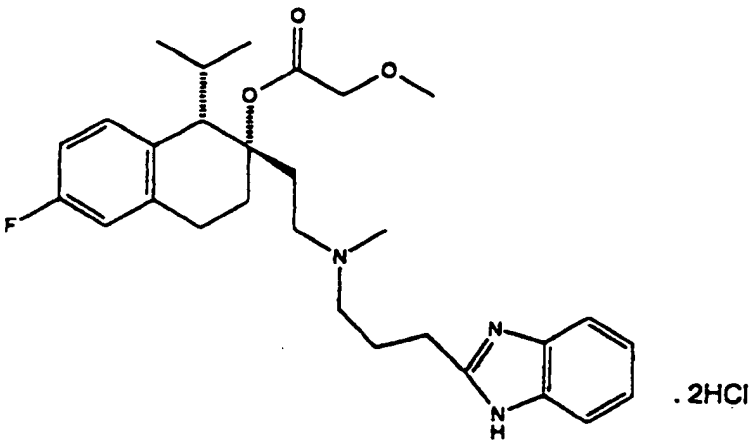
exhibit (1)

(Roche Hexagon)

POSICOR®
(mibefradil dihydrochloride)
TABLETS

DESCRIPTION: POSICOR® (mibefradil dihydrochloride) is a selective T-type calcium channel ion influx inhibitor.

Mibefradil dihydrochloride is a pure enantiomer and belongs to the class of tetralol calcium antagonists. Its chemical name is (1S, 2S)-2-[2[[3-2-benzimidazoyl) propyl] methylamino] ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride, its empirical formula is $C_{29}H_{38}FN_3O_3$ .2HCl, its molecular weight is 568.56, and its structural formula is:



. 2HCl

Mibefradil dihydrochloride is a white to off-white crystalline powder. It is readily soluble in water.

In addition to the active ingredient mibefradil dihydrochloride, each tablet contains the following inactive ingredients: lactose anhydrous, corn starch, polyvinylpyrrolidone, talc, sodium stearyl fumarate, hydroxypropyl methylcellulose, ethyl cellulose, triacetin and titanium dioxide, with synthetic yellow iron oxide (50 mg tablet) and synthetic red iron oxides (100 mg tablet).

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** At therapeutic concentrations, mibefradil blocks both the T-type (low-voltage) and L-type (high-voltage) calcium channels, with greater selectivity for T-type channels, in contrast to benzothiazepine, dihydropyridine, and phenylalkylamine calcium antagonists, which at therapeutic concentrations block only the L-type channels. The binding site of mibefradil is different from that of the dihydropyridines.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. In vitro, mibefradil selectively inhibits calcium ion influx across cell membranes of cardiac and vascular smooth muscle with a pronounced dependence on membrane potential. The dose and concentration ranges for vasodilation were lower than, and clearly distinct from, the ranges where a decrease in cardiac contractility was observed. This was observed both in vivo and in vitro and in both normal animals and in animal models of heart failure. Although in in vitro tissue preparations mibefradil was negatively inotropic at high concentrations, negative inotropic effects

could be demonstrated in intact animals only at very high doses, well outside the therapeutic range.

Mibefradil does not induce reflex tachycardia, but rather causes a slight reduction in heart rate.

Serum calcium concentration was not affected by mibefradil.

Hypertension: Mibefradil is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance, and thereby a reduction in blood pressure.

Chronic Stable Angina Pectoris: The precise mechanism by which mibefradil reduces angina has not been fully elucidated but is thought to involve reduction in heart rate, total peripheral resistance (afterload), and double product (heart rate x systolic blood pressure) at any given level of exercise, resulting in a decrease in cardiac workload and myocardial oxygen demand.

Pharmacokinetics and Metabolism: After oral administration of POSICOR, peak plasma levels of mibefradil are reached within one to two hours after administration. Bioavailability of a single oral dose of mibefradil within the therapeutic range was 70%. The proportion of mibefradil metabolized before reaching the systemic circulation (first-pass metabolism) is reduced after chronic dosing and bioavailability is about 90% at steady state. The presence of food has no effect on rate and extent of absorption of mibefradil. Mean elimination half-life following chronic dosing is 17 to 25 hours. During once-daily dosing, steady-state conditions are reached within three to four days. Plasma AUCs are proportional to dose in the therapeutic range.

Distribution: Volume of distribution at steady-state (V_{ss}) ranges from 130 to 190 L. Mibefradil is highly bound to plasma proteins ($\geq$ 99% at therapeutic concentrations), principally to alpha$_1$-acid glycoprotein.

Metabolism: Metabolism of mibefradil is mediated by two pathways: esterase catalyzed hydrolysis of the ester side chain to yield an alcohol metabolite and cytochrome P450 (3A4) catalyzed oxidation. After chronic dosing, the oxidative pathway becomes less important and the plasma level of the alcohol metabolite of mibefradil increases. In animal models the pharmacological effect of this alcohol metabolite was about 10% of the parent compound. At steady state, plasma concentrations of the metabolite exceed those of parent mibefradil after 100 mg doses.

Excretion: After metabolic inactivation, mibefradil is excreted into the bile (75%) and urine (25%). Less than 3% of mibefradil is excreted unchanged into the urine. No clinically relevant influence of demographic factors (age, race, gender, body weight) on clearance has been found.

Special Populations: Congestive Heart Failure: There is no evidence for a change in the pharmacokinetics of mibefradil in patients with congestive heart failure.

Hepatic Insufficiency: No clinically relevant change in the pharmacokinetics of mibefradil in patients with impaired liver function was observed after single doses of 100 mg POSICOR. As mibefradil is completely metabolized and eliminated mainly via the biliary route, however,

monitoring of blood pressure and heart rate is advised when administering POSICOR to patients with severe hepatic impairment.

Chronic Renal Failure: Pharmacokinetics of mibefradil are unchanged in patients with chronic renal failure. Mibefradil is not removed by dialysis.

Gender/Race: No clinically relevant difference in the pharmacokinetics of mibefradil was observed between either men and women or between blacks and non-blacks.

Pediatrics: No studies have been conducted in pediatric patients.

Geriatrics: Population kinetics in 315 patients (151 ≥ 65 years) indicated that there was no change in the pharmacokinetics of mibefradil with age.

Drug Interactions: See PRECAUTIONS.

Pharmacodynamics: The plasma concentrations of mibefradil are predictive of its pharmacological effects.

Hemodynamics: Following administration of mibefradil to patients with hypertension, POSICOR produces a dose-related and plasma concentration-related reduction of supine, sitting and standing blood pressure, without postural dysregulation. These decreases in blood pressure following multiple dosing are accompanied by a slight increase in cardiac output with a small, dose-dependent decrease in heart rate. The magnitude of the blood pressure reduction depends on initial blood pressure; the higher the initial blood pressure, the greater the effect.

Blood pressure lowering effect is maintained for 24 hours following chronic oral administration of POSICOR. Normotensive subjects experienced no clinically relevant change in blood pressure after chronic dosing with 50 mg to 100 mg mibefradil. The reduction in heart rate seen with mibefradil depends on the initial heart rate; the lower the initial heart rate, the smaller the effect. The concentration effect relationship was not influenced by demographic factors (age, race, gender).

Electrophysiology: Mibefradil affects the sinus and atrioventricular nodes, resulting in a slight dose dependent slowing of heart rate and a small increase in PR interval. In placebo-controlled clinical trials in patients with hypertension or chronic stable angina pectoris, the mean decreases in heart rate were about 5 and 9 beats per minute (bpm) with 50 mg (N=279) and 100 mg (N=285) of POSICOR, respectively. In these patients, the mean increase in PR interval was 3.3 msec (50 mg) and 9.7 msec (100 mg). The increases, compared to placebo, of the rate of first-degree AV block (PR interval > 200 msec) were 1.1% at 50 mg, 7.4% at 100 mg and 9.1% at 150/200 mg. The rates of sinus bradycardia (heart rate < 45 bpm) were 0.7% at 50 mg, 1.4% at 100 mg and 3.8% at 150/200 mg. In 2636 patients with hypertension or chronic stable angina pectoris, treatment with POSICOR 50 mg or 100 mg was rarely associated with second-degree AV block (6 patients, 0.2%) and there were no reports of third-degree AV block.

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The effects of mibefradil on the conduction system were evaluated in 71 patients in a placebo-controlled trial. Mibefradil was administered IV at doses that produced plasma concentrations seen following oral administration of mibefradil at 50 mg and 100 mg. In this study, mibefradil slightly lengthened the corrected sinus node recovery time and AH interval and raised the Wenckebach point. Atrial effective and functional refractory periods, AV node functional and effective refractory periods and the conduction time in the His-Purkinje system and ventricular tissue were not affected.

Mibefradil causes dose-related flattening of the T wave and an increase in the voltage of the U wave. The U wave can sometimes become so large that it merges with the flattened T wave, and the resulting pattern has sometimes been misread (by both automated electrocardiographic interpreters and clinicians) as QTc prolongation.

The exact definition of this phenomenon is arbitrary. Changes sufficient to be misread as QTc prolongation in clinical trials did not occur at the therapeutic doses of 50 mg or 100 mg of mibefradil but were observed in 1% of patients who received 150 mg and 5.4% of patients who received 200 mg, both of which are above the recommended doses. Similar patterns have been seen in subjects treated with high and supratherapeutic doses of diltiazem and verapamil.

The addition of POSICOR to chronic beta-blocker treatment was evaluated in both hypertensive and chronic stable angina pectoris patients (195 patients) and was associated with changes in heart rate and PR interval similar to those seen in patients treated with mibefradil alone. There were no cases of second- or third-degree AV block in these patients. In 44 angina patients treated with POSICOR and beta-blockers, no acute withdrawal effects, such as worsening of angina or palpitations, were seen upon beta-blocker discontinuation.

The combination of POSICOR and digoxin was not associated with an additional prolongation of PR time beyond the effect of POSICOR alone.

Effects in Hypertension: The antihypertensive effects of POSICOR were demonstrated in four placebo-controlled, double-blind, randomized trials conducted for 4 to 14 weeks, three in patients receiving no other treatment and one in patients still hypertensive while receiving 25 mg of hydrochlorothiazide. These involved 1123 patients with hypertension (933 on POSICOR and 190 on placebo). Once-daily administration of 50 mg and 100 mg was consistently associated with clinically and statistically significant reductions in both systolic and diastolic blood pressure. The mean differences from placebo in systolic/diastolic blood pressure at trough (24 hours post dose), for the 50 mg and 100 mg doses were about 7-11/5-7 and 7-10/9-11 mmHg, respectively. The antihypertensive effect of POSICOR was present in the sitting, standing and supine positions. The antihypertensive effect was not associated with reflex tachycardia, but rather a slight decrease in heart rate. The blood pressure was controlled over the 24-hour dosing interval, with little difference between trough and peak effect (trough to peak ratio >75%). A modest effect was seen on Day 1, and the full antihypertensive effect was reached within one to two weeks.

Long-term antihypertensive effects were demonstrated in two four-month, randomized, placebo-controlled withdrawal studies involving 221 patients on mibefradil. Blood pressure returned to approximately pretreatment levels in four weeks. Thus, there was no tolerance (loss of efficacy)

observed on long-term administration. Additionally, no rebound increase in blood pressure was seen on discontinuation of POSICOR.

The antihypertensive effects of POSICOR were similar regardless of race, gender, body weight, history of diabetes mellitus or history of coronary artery disease. POSICOR was effective in lowering high blood pressure in patients with chronic renal failure complicated by systemic hypertension. Additive antihypertensive effects have been observed in clinical trials where POSICOR was combined with diuretics, ACE inhibitors and beta-blockers.

Effects in Chronic Stable Angina Pectoris: The antianginal and antiischemic efficacy of POSICOR was demonstrated in five placebo-controlled, double-blind, randomized trials, involving 870 patients with chronic stable angina pectoris, 564 on POSICOR and 306 on placebo. Once-daily administration of 100 mg was associated with statistically significant increases in all exercise test parameters, in all studies, but the effect of 50 mg was smaller and less consistent. The increases in symptom-limited exercise duration at trough (24 hours post dose) for POSICOR 50 mg and 100 mg were about 20 seconds (seen in two of three studies) and about 50 seconds (in all three studies), respectively. In these studies, POSICOR also significantly delayed the time to onset of angina during exercise and, in a pooled analysis, decreased the rate of anginal attacks and nitroglycerin consumption reported by the patients. Additionally, POSICOR significantly delayed the onset of ischemia (persistent 1mm ST segment depression) during exercise in all placebo-controlled studies. These antianginal and antiischemic effects were associated with a dose-dependent mean decrease in double product for any given level of exercise (heart rate x systolic blood pressure), mainly due to a decrease in heart rate.

Long-term improvements in exercise test parameters were demonstrated in a four-month, randomized, placebo-controlled withdrawal study involving 102 patients on mibefradil. Thus, there was no tolerance (loss of efficacy) observed on long-term administration. Additionally, no rebound increase in anginal symptomatology was seen on discontinuation of POSICOR.

The antianginal effects of POSICOR were similar regardless of gender, race, body weight or history of hypertension, diabetes mellitus, myocardial infarction, PTCA or CABG. Improvements in all exercise test parameters and anginal symptomatology were observed in three placebo-controlled, double-blind, randomized clinical trials in which POSICOR was added to therapy with beta-blockers or long-acting nitrates.

INDICATIONS AND USAGE: *Hypertension:* POSICOR is indicated for the treatment of hypertension. POSICOR can be used alone or in combination with other antihypertensive agents.

Chronic Stable Angina Pectoris: POSICOR is indicated for the treatment of chronic stable angina pectoris. POSICOR can be used alone or in combination with other antianginal drugs.

CONTRAINDICATIONS: POSICOR is contraindicated in patients with:

1. Sick sinus syndrome or second- or third-degree AV block, without a pacemaker;

2. A known sensitivity to mibefradil;

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3. Coadministration of terfenadine, astemizole and cisapride.

WARNING: As described in the CLINICAL PHARMACOLOGY section, mibefradil may cause dose-related changes in the appearance of the electrocardiographic T and U waves. These changes may interfere with measurement of the QTc interval. Some drugs (eg, quinidine, sotalol) are sometimes monitored by following the QTc interval on serial electrocardiograms, in order to reduce the risk of torsades de pointes and other malignant arrhythmias. When mibefradil is coadministered with these drugs, it may be difficult to utilize serial electrocardiograms for this purpose.

PRECAUTIONS: *General:* POSICOR inhibits cytochrome P450 2D6 and 3A4 and can interact with many concomitant drugs, increasing their plasma concentrations (see *Drug Interactions*).

Hypotension: Although hypotension, postural hypotension, and syncope have been only rarely associated with POSICOR, and are not clearly more common than with placebo, caution should be exercised when administering POSICOR, particularly to patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Acute hemodynamic studies in a small number of patients with ischemic heart disease with or without impaired cardiac function treated with POSICOR have not demonstrated negative inotropic effects, nor was POSICOR associated with reflex tachycardia or an increase in neurohormones. Long-term studies in patients with moderate to severe (NYHA III, IV) heart failure have not been carried out. As with all calcium antagonists, caution should be exercised when treating patients with heart failure or compromised ventricular function.

Patients with Hepatic Failure: Since mibefradil is extensively metabolized by the liver, caution should be exercised when administering POSICOR to patients with severe hepatic impairment.

Cardiac Conduction: As described under CLINICAL PHARMACOLOGY, POSICOR slows sinus and AV node conduction, sometimes resulting in abnormally low heart rates; 0.7% and 1.4% of patients had heart rates below 45 bpm on 50 mg and 100 mg, respectively. Therefore, patients with a pretreatment heart rate below 50 bpm should be followed closely. Treatment with POSICOR has rarely been associated with second-degree AV block, 0.2% of patients on doses of 50 mg to 100 mg. No cases of third-degree AV block have been reported at 50 mg to 100 mg, but at higher doses third-degree AV block can rarely occur.

Drug Interactions: *Effects of Other Drugs on Mibefradil Pharmacokinetics:* No clinically relevant changes in pharmacokinetics of mibefradil have been seen in specific studies when mibefradil was coadministered with enalapril, atenolol, metoprolol, theophylline and cimetidine.

Effects of Mibefradil on the Pharmacokinetics of Other Drugs: **Interactions with Drugs Metabolized by Cytochrome P450 Enzymes:** In vitro results indicate that some isozymes of the cytochrome P450 enzyme system, including 2D6, 1A2, and 3A4, are inhibited in the presence of mibefradil or its metabolites. Coadministration of POSICOR with drugs metabolized by these isozymes may result in increased plasma concentrations of these drugs.

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Drugs Metabolized by Cytochrome P450 2D6: A subset (about 7%) of the white population and 1% and 2% of Orientals and blacks, respectively, have reduced activity of the drug-metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase). Such individuals are referred to as "poor metabolizers" of such drugs as dextromethorphan, the type 1C antiarrhythmics propafenone, flecainamide and mexiletine, some beta-blockers and tricyclic antidepressants (particularly those with high first-pass effect, ie, desipramine and imipramine). Poor metabolizers have higher than expected plasma concentrations of such drugs when given in usual doses. Depending on the fraction of the drug metabolized by cytochrome P450 2D6, the increase in plasma concentration may be small or quite large. POSICOR, like several other drugs, inhibits the activity of this isozyme and can make previously normal metabolizers resemble poor metabolizers. Concomitant use of POSICOR with drugs metabolized by cytochrome P450 2D6 may require dose adjustment of the other drugs.

Tricyclic Antidepressants: Imipramine and desipramine have been shown to have substantial (seven- to eightfold) increases in AUC when CYP 450 2D6 metabolism is inhibited; concomitant use of tricyclic antidepressants with POSICOR would require substantial dose adjustment of the tricyclic antidepressant.

Drugs Metabolized by Cytochrome P450 3A4: POSICOR and/or its metabolites also inhibit the activity of cytochrome P450 3A4, an enzyme responsible for the metabolism of many drugs, including quinidine, short-acting benzodiazepines, most calcium-channel blockers, terfenadine astemizole and cisapride. POSICOR may increase plasma concentrations of coadministered drugs that are primarily metabolized by the cytochrome P450 3A4 enzyme system and may consequently increase or prolong their therapeutic and adverse effects. Therefore, unless otherwise specified, dosage adjustment of these drugs may be necessary. For drugs that can cause serious adverse effects if concentration is increased, concomitant use with POSICOR should be avoided (see CONTRAINDICATIONS).

The following drug interactions have been identified involving mibefradil and other drugs metabolized by the cytochrome P450 system:

Terfenadine: Coadministration of terfenadine (metabolized by CYP 450 3A4) with POSICOR in healthy subjects led to elevated plasma concentrations of terfenadine up to 40 ng/mL with twice-daily dosing of 60 mg terfenadine, resulting in a 12% increase in mean QTc interval. Since QTc prolongation due to elevated plasma concentrations of terfenadine can be associated with life-threatening cardiac dysrhythmias and death, coadministration of POSICOR with terfenadine is contraindicated (see CONTRAINDICATIONS).

Astemizole and Cisapride: Although there are no specific studies of interaction of mibefradil with these drugs, substantial inhibition of their metabolism would be expected. Since elevated plasma concentrations of astemizole and cisapride can be associated with life-threatening cardiac dysrhythmias, their use with mibefradil is contraindicated. One such case has been observed in a patient receiving cisapride and concomitant mibefradil.

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Cyclosporine A: Cyclosporine A (Sandimmune®), a drug metabolized by CYP 450 3A4, levels increased about twofold under concomitant treatment with 50 mg POSICOR for eight days. Therefore, cyclosporine A levels should be monitored and its dose adjusted accordingly.

Quinidine: In healthy volunteers, elevations in peak quinidine plasma concentrations (15% to 19%) and AUC (50%) were found during coadministration of single doses of quinidine with POSICOR 50 mg and 100 mg, but the active metabolite of quinidine was markedly reduced. No clinically relevant pharmacodynamic interactions were observed.

Metoprolol: Coadministration of POSICOR with metoprolol (metabolized by CYP 450 2D6) in healthy subjects resulted in a twofold increase in peak plasma concentrations of total (R- and S-enantiomeric) metoprolol and about four- to fivefold increase in AUC. Elimination half-life increased from three hours to seven to eight hours. The increase in the pharmacologically more active S-isomer, however, is only about 30%, so that little pharmacologic effect or effect on cardioselectivity would be expected with concomitant POSICOR.

Other Information: In clinical studies, POSICOR has been administered without apparent harm with commonly used drugs including diuretics, beta-blockers, ACE inhibitors, nonsteroidal antiinflammatory drugs, long-acting nitrates, sublingual nitroglycerin, oral hypoglycemics, fibrate lipid-lowering agents, conjugated estrogens, antibiotics and antithrombotics. CYP 450 3A4 mediates the metabolism of several HMG CoA reductase inhibitors. Use of these drugs has been associated with rhabdomyolysis, which may be more frequent when they are coadministered with drugs that inhibit CYP 450 3A4. Although no such adverse interaction has been seen with POSICOR, the possibility should be considered.

Specific Interaction Studies: In specific studies, no clinically relevant interactions have been observed between the recommended doses of POSICOR and enalapril, atenolol or cimetidine. Despite in vitro evidence of inhibition of CYP 450 1A2, no pharmacokinetic interaction was observed with theophylline, a CYP 450 1A2 substrate. In healthy volunteers, small elevations in digoxin peak plasma levels (20% to 30%) were found during coadministration with POSICOR 50 mg and 100 mg, but trough plasma levels were unchanged in these volunteers and in patients with congestive heart failure.

Protein Binding: Mibefradil is highly protein bound (99.5%), mainly to alpha$_1$-acid glycoprotein (95%). Therefore, it will not displace drugs which bind to serum albumin, such as warfarin, phenytoin and digoxin.

Information for Patients: Patients should be instructed to take POSICOR whole and not to crush or chew the tablet. Patients should inform their physicians if they are pregnant or plan to become pregnant or are breastfeeding. Patients should be informed that light-headedness or fatigue can occur and that these symptoms should be reported to a physician.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Mibefradil was not mutagenic in the Ames microbial mutagenicity test with or without metabolic activation, in the microbial test with E. coli or in Chinese hamster V79 cells. No genotoxicity was observed in a test of unscheduled

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DNA synthesis in rat primary hepatocytes, and no chromosomal damage was observed in a test of human peripheral blood lymphocytes treated in vitro or in an in vivo micronucleus test.

A decrease in mating incidence and a prolongation of time to mating was observed when male and female rats were treated with mibefradil dihydrochloride at a daily dose of 39 mg mibefradil/kg (approximately three times the maximum recommended human dose [MRHD] on a mg/m^2 basis) prior to and during the mating period. For those females successfully mated at this dose, there was a decrease in fetuses/dam observed at caesarean section or pups/dam at natural delivery, findings associated with both a decrease in number of corpora lutea per dam (evidence of a decrease in ovulation) and an increase in preimplantation loss (ovulations not resulting in implants).

Oral gavage administration of mibefradil dihydrochloride to male mice for up to 95 weeks and to female mice for up to 104 weeks at doses up to 65 mg mibefradil/kg/day (about three times the MRHD of 100 mg mibefradil/day on a mg/m^2 basis) revealed no evidence of a carcinogenic effect of mibefradil. When administered in the feed of rats at doses of 35 mg mibefradil/kg/day (about three times the MRHD on a mg/m^2 basis) for up to 104 weeks, an increased incidence of squamous cell carcinoma of the oral cavity was observed. A similar association was observed when another rat study was conducted with similar doses of mibefradil administered by gavage. The latter study, which evaluated diet as a risk factor for the oral cavity tumors, demonstrated that the carcinogenic effect of mibefradil was dependent on the aggressiveness (in terms of producing severe periodontitis) of the diet employed combined with class-related gingival overgrowth. No tumors were observed when mibefradil was administered to rats fed a less aggressive diet associated with much lower levels of periodontitis.

Pregnancy: Pregnancy Category C. Developmental toxicity studies have been conducted in rats and rabbits. In rabbits, no adverse effects on development were seen with doses up to 35 mg mibefradil/kg/day (approximately seven times the MRHD on a mg/m^2 basis). In rats there was an increased incidence of fetuses with cardiovascular abnormalities at 39 mg/kg/day (approximately three times the MRHD). Skeletal and visceral defects have been observed following the administration of other calcium antagonists to pregnant rodents or rabbits. There are no adequate and well-controlled studies in pregnant women. POSICOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: Dystocia and/or prolongation of pregnancy, which was associated with uterine prolapse, stillbirths and neonatal mortality, was observed to occur when mibefradil dihydrochloride was administered to pregnant rats, during the expected time of parturition, at 13 or more mg mibefradil/kg/day (13 mg/kg/day is approximately equal to the MRHD on a mg/m^2 basis). Calcium-channel blocking agents have been shown to inhibit uterine contraction in rats, rabbits and humans, presumably by inhibition of Ca^{++} influx in the myometrium. POSICOR should be avoided during the time of expected labor and during parturition.

Nursing Mothers: When mibefradil was administered to lactating rats, their milk attained mibefradil concentrations two to five times greater than those in their serum. If mibefradil enters human milk in similar quantities, then a human infant ingesting such milk would (scaling directly by weight) be expected to develop serum mibefradil levels somewhat less than those of the

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mother. On the other hand, mibefradil levels have not been measured in human milk. The pharmacokinetics and pharmacodynamics of mibefradil in human infants have not been studied, and neonates have been reported to be disproportionately sensitive to some other calcium-channel blockers. Administration of mibefradil should therefore be avoided, if possible, in lactating women who continue to nurse.

Pediatric Use: Safety and effectiveness of POSICOR in pediatric patients have not been established.

ADVERSE REACTIONS: POSICOR has been evaluated for safety in 3430 patients (2194 with hypertension, 1236 with chronic stable angina pectoris). In general, treatment with POSICOR was well tolerated at doses up to 100 mg daily. Most adverse reactions associated with POSICOR were transient and of mild or moderate intensity. In placebo-controlled clinical trials, the rate of discontinuation of POSICOR (50 mg and 100 mg) due to adverse reactions was similar to that of placebo. Discontinuation due to dizziness was the only reason for premature withdrawal that was more common on mibefradil than on placebo. In the pooled placebo-controlled hypertension and chronic stable angina pectoris trials that studied doses of 50 mg/day and 100 mg/day, the incidence of adverse experiences present in at least 1% of patients treated with the 100 mg dose and more common on that dose than on placebo were:

	Placebo	POSICOR	
		50 mg	100 mg
	(N=283)	(N=279)	(N=285)
Headache	6%	3%	8%
Leg Edema	3%	1%	4%
Rhinitis	0%	3%	3%
Abdominal Pain	1%	1%	2%
Light-headed Feeling	0%	1%	3%
Dyspepsia	1%	1%	2%

The following adverse experiences were also present in >1% of patients treated with the 100 mg dose but occurred at a frequency equal to or less than placebo: allergic reaction, angina pectoris, dizziness, fatigue, flushing, influenza, palpitations, upper respiratory tract infection and vomiting/nausea.

The following adverse experiences occurred in a dose-related manner in placebo-controlled trials over a dose range of 50 mg to 150 mg: dizziness, dyspepsia, flushing, leg edema, rhinitis and vomiting/nausea.

There were no clinically important differences in the effect of POSICOR on adverse experience rates based on age, gender or race.

In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, the following adverse experiences, whether drug related or not, occurred at a frequency greater than 0.5% or occurred at a lower rate but were potentially important:

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Autonomic Nervous System: increased sweating, orthostatic complaints, postural hypotension, syncope

Body as a Whole: generalized weakness, trauma

Cardiovascular: bradycardia, cardiac failure, chest pain nonspecific, hypotension

Central and Peripheral Nervous System: paresthesia

Gastrointestinal: constipation, diarrhea, flatulence, gastroenteritis, rectal hemorrhage

Hearing and Vestibular: ear buzzing, otitis

Immunologic: angioedema

Musculoskeletal: arthritis, back pain, chest pain, muscle cramps, pain of extremities, sprains and strains

Psychiatric: anxiety, depression, insomnia

Reproductive, Male: impotence

Respiratory: bronchitis, coughing, dyspnea, nasal congestion, pharyngitis, sinusitis

Skin and Appendages: exfoliative dermatitis, rash

Urinary System: urinary tract infection

Vision: conjunctivitis

Electrocardiographic Changes: Treatment emergent ECG changes that clearly occurred in a dose-related manner in the placebo-controlled trials were bradycardia (heart rate < 45 bpm): 0.7% (50 mg) and 1.4% (100 mg) and first-degree AV block: 3.6% (50 mg) and 8.4% (100 mg). In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, second-degree AV block was recorded in 0.2% of the patients.

POSICOR therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in hematology parameters, serum potassium, sodium, calcium, glucose, plasma lipids, uric acid, urea nitrogen, creatinine or liver function tests.

OVERDOSAGE: At present there has been no experience with single doses >350 mg or multiple doses >250 mg. Doses higher than these might cause excessive peripheral vasodilation with marked hypotension, bradycardia and/or high-degree AV block. If a patient is suspected of having taken an overdose, continuous ECG monitoring and repeated blood pressure measurements should be instituted. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these measures, administration of vasopressors (such as phenylephrine) should be

considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium antagonists. As mibefradil is highly bound to plasma proteins, it cannot be removed by dialysis.

Bradycardia and high-degree AV block may be treated with atropine, isoproterenol and cardiac pacing.

DOSAGE AND ADMINISTRATION: The recommended doses of POSICOR are 50 mg and 100 mg once daily. The larger dose is, on average, more effective. Doses above 100 mg offer little or no additional benefit and induce a greater rate of adverse reactions. POSICOR can be taken with or without food. Tablets should be swallowed and not chewed or crushed.

Hypertension: The recommended initial dose of POSICOR is 50 mg once daily. Titration to 100 mg once daily should be based on blood pressure response; the full effect of a given dose level is generally seen after one to two weeks. The same dosage recommendations apply for all populations, including elderly patients and patients with chronic renal failure. However, caution should be exercised in patients with severe hepatic impairment.

Chronic Stable Angina Pectoris: The recommended initial dose of POSICOR is 50 mg once daily. Titration to 100 mg once daily should be based on therapeutic response. The same dosage recommendations apply for all populations, including elderly patients and patients with chronic renal failure. However, caution should be exercised in patients with severe hepatic impairment.

Coadministration with Other Antihypertensive and/or Antianginal Drugs: POSICOR has been safely administered with diuretics, ACE inhibitors, beta-blockers, long-acting nitrates and sublingual nitroglycerin.

Administration in Subpopulations: POSICOR has been used safely in patients regardless of demographic factors (age, race, gender, body weight) and common concomitant diseases, such as chronic renal failure, chronic obstructive pulmonary disease and diabetes mellitus.

HOW SUPPLIED: POSICOR is supplied as biconvex, hexagonal tablets, available in bottles and Tel-E-Dose® packages as follows:

	50 mg	100 mg
color	pale yellow	light orange
engraving	ROCHE POSICOR 50	ROCHE POSICOR 100
bottle of 100	NDC 0004-0080-01	NDC 0004-0081-01
bottle of 300	NDC 0004-0080-27	– – –
Tel-E-Dose® of 100	NDC 0004-0080-49	NDC 0004-0081-49

Storage Conditions: Store at 15° to 30°C (59° to 86°F) in tight containers as defined in USP/NF.

POSICOR® (mibefradil dihydrochloride)

(Roche Hexagon)

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

25995005-0697

Issued: June 1997
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exhibit (2)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-689

JUN 20 1997

Hoffmann-La Roche, Inc.
Attention: Mr. Rudolph W. Lucek
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Lucek:

Please refer to your March 8, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Posicor (mibefradil dihydrochloride) Tablets, 50 and 100 mg.

We acknowledge receipt of your amendments dated April 15 and 22, and June 13 and 19 (two), 1997.

This new drug application provides for the use of Posicor (mibefradil dihydrochloride) Tablets for the treatment of hypertension and chronic stable angina pectoris.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-689. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment specified in your submission of June 13, 1997. This commitment and its associated schedule for completion is as follows:

> You will conduct a pharmacokinetic interaction study between mibefradil and a tricyclic antidepressant metabolized by cytochrome P450 2D6. The projected completion date for this study is the second quarter of 1998.

Protocols, data, and final reports should be submitted to IND 39,901 for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment, submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly labeled "Phase 4 Commitment." In addition, we request that each annual report to this NDA include a section that summarizes the status of this Phase 4 commitment, identifying each submission and its related commitment. If you believe the situation has changed and the data a Phase 4 study was designed to provide are no longer necessary, fully explain why you believe you should be released from the commitment. All annual reports to this NDA should include an update on Phase 4 studies until you are notified that we consider all commitments to have been satisfactorily fulfilled or canceled.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

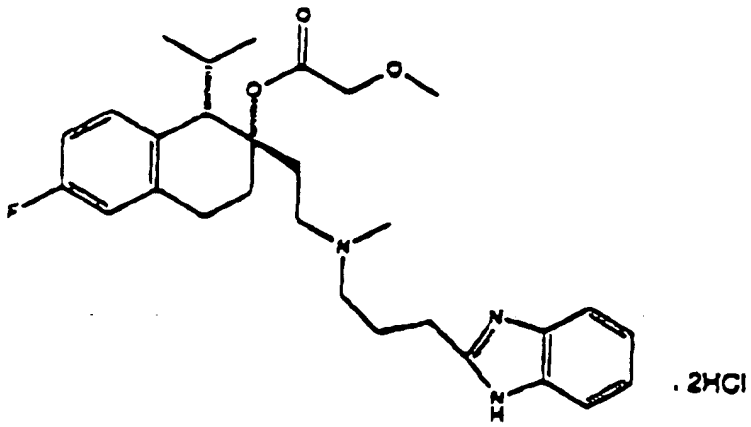
Enclosure

(Roche Hexagon)

POSICOR®
(mibefradil dihydrochloride)
TABLETS

DESCRIPTION: POSICOR® (mibefradil dihydrochloride) is a selective T-type calcium channel ion influx inhibitor.

Mibefradil dihydrochloride is a pure enantiomer and belongs to the class of tetralol calcium antagonists. Its chemical name is (1S, 2S)-2-[2[[3-2-benzimidazoyl) propyl] methylamino] ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride, its empirical formula is $C_{29}H_{38}FN_3O_3 \cdot 2HCl$, its molecular weight is 568.56, and its structural formula is:



Mibefradil dihydrochloride is a white to off-white crystalline powder. It is readily soluble in water.

In addition to the active ingredient mibefradil dihydrochloride, each tablet contains the following inactive ingredients: lactose anhydrous, corn starch, polyvinylpyrrolidone, talc, sodium stearyl fumarate, hydroxypropyl methylcellulose, ethyl cellulose, triacetin and titanium dioxide, with synthetic yellow iron oxide (50 mg tablet) and synthetic red iron oxides (100 mg tablet).

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** At therapeutic concentrations, mibefradil blocks both the T-type (low-voltage) and L-type (high-voltage) calcium channels, with greater selectivity for T-type channels, in contrast to benzothiazepine, dihydropyridine, and phenylalkylamine calcium antagonists, which at therapeutic concentrations block only the L-type channels. The binding site of mibefradil is different from that of the dihydropyridines.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. In vitro, mibefradil selectively inhibits calcium ion influx across cell membranes of cardiac and vascular smooth muscle with a pronounced dependence on membrane potential. The dose and concentration ranges for vasodilation were lower than, and clearly distinct from, the ranges where a decrease in cardiac contractility was observed. This was observed both in vivo and in vitro and in both normal animals and in animal models of heart failure. Although in in vitro tissue preparations mibefradil

POSICOR® (mibefradil dihydrochloride)

was negatively inotropic at high concentrations, negative inotropic effects could be demonstrated in intact animals only at very high doses, well outside the therapeutic range.

Mibefradil does not induce reflex tachycardia, but rather causes a slight reduction in heart rate.

Serum calcium concentration was not affected by mibefradil.

Hypertension: Mibefradil is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance, and thereby a reduction in blood pressure.

Chronic Stable Angina Pectoris: The precise mechanism by which mibefradil reduces angina has not been fully elucidated but is thought to involve reduction in heart rate, total peripheral resistance (afterload), and double product (heart rate x systolic blood pressure) at any given level of exercise, resulting in a decrease in cardiac workload and myocardial oxygen demand.

Pharmacokinetics and Metabolism: After oral administration of POSICOR, peak plasma levels of mibefradil are reached within one to two hours after administration. Bioavailability of a single oral dose of mibefradil within the therapeutic range was 70%. The proportion of mibefradil metabolized before reaching the systemic circulation (first-pass metabolism) is reduced after chronic dosing and bioavailability is about 90% at steady state. The presence of food has no effect on rate and extent of absorption of mibefradil. Mean elimination half-life following chronic dosing is 17 to 25 hours. During once-daily dosing, steady-state conditions are reached within three to four days. Plasma AUCs are proportional to dose in the therapeutic range.

Distribution: Volume of distribution at steady-state (V_{ss}) ranges from 130 to 190 L. Mibefradil is highly bound to plasma proteins (≥ 99% at therapeutic concentrations), principally to alpha$_1$-acid glycoprotein.

Metabolism: Metabolism of mibefradil is mediated by two pathways: esterase catalyzed hydrolysis of the ester side chain to yield an alcohol metabolite and cytochrome P450 (3A4) catalyzed oxidation. After chronic dosing, the oxidative pathway becomes less important and the plasma level of the alcohol metabolite of mibefradil increases. In animal models the pharmacological effect of this alcohol metabolite was about 10% of the parent compound. At steady state, plasma concentrations of the metabolite exceed those of parent mibefradil after 100 mg doses.

Excretion: After metabolic inactivation, mibefradil is excreted into the bile (75%) and urine (25%). Less than 3% of mibefradil is excreted unchanged into the urine. No clinically relevant influence of demographic factors (age, race, gender, body weight) on clearance has been found.

Special Populations: Congestive Heart Failure: There is no evidence for a change in the pharmacokinetics of mibefradil in patients with congestive heart failure.

Hepatic Insufficiency: No clinically relevant change in the pharmacokinetics of mibefradil in patients with impaired liver function was observed after single doses of 100 mg POSICOR. As mibefradil is completely metabolized and eliminated mainly via the biliary route, however,

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monitoring of blood pressure and heart rate is advised when administering POSICOR to patients with severe hepatic impairment.

Chronic Renal Failure: Pharmacokinetics of mibefradil are unchanged in patients with chronic renal failure. Mibefradil is not removed by dialysis.

Gender/Race: No clinically relevant difference in the pharmacokinetics of mibefradil was observed between either men and women or between blacks and non-blacks.

Pediatrics: No studies have been conducted in pediatric patients.

Geriatrics: Population kinetics in 315 patients (151 ≥ 65 years) indicated that there was no change in the pharmacokinetics of mibefradil with age.

Drug Interactions: See PRECAUTIONS.

Pharmacodynamics: The plasma concentrations of mibefradil are predictive of its pharmacological effects.

Hemodynamics: Following administration of mibefradil to patients with hypertension, POSICOR produces a dose-related and plasma concentration-related reduction of supine, sitting and standing blood pressure, without postural dysregulation. These decreases in blood pressure following multiple dosing are accompanied by a slight increase in cardiac output with a small, dose-dependent decrease in heart rate. The magnitude of the blood pressure reduction depends on initial blood pressure; the higher the initial blood pressure, the greater the effect.

Blood pressure lowering effect is maintained for 24 hours following chronic oral administration of POSICOR. Normotensive subjects experienced no clinically relevant change in blood pressure after chronic dosing with 50 mg to 100 mg mibefradil. The reduction in heart rate seen with mibefradil depends on the initial heart rate; the lower the initial heart rate, the smaller the effect. The concentration effect relationship was not influenced by demographic factors (age, race, gender).

Electrophysiology: Mibefradil affects the sinus and atrioventricular nodes, resulting in a slight dose dependent slowing of heart rate and a small increase in PR interval. In placebo-controlled clinical trials in patients with hypertension or chronic stable angina pectoris, the mean decreases in heart rate were about 5 and 9 beats per minute (bpm) with 50 mg (N=279) and 100 mg (N=285) of POSICOR, respectively. In these patients, the mean increase in PR interval was 3.3 msec (50 mg) and 9.7 msec (100 mg). The increases, compared to placebo, of the rate of first-degree AV block (PR interval > 200 msec) were 1.1% at 50 mg, 7.4% at 100 mg and 9.1% at 150/200 mg. The rates of sinus bradycardia (heart rate < 45 bpm) were 0.7% at 50 mg, 1.4% at 100 mg and 3.8% at 150/200 mg. In 2636 patients with hypertension or chronic stable angina pectoris, treatment with POSICOR 50 mg or 100 mg was rarely associated with second-degree AV block (6 patients, 0.2%) and there were no reports of third-degree AV block.

The effects of mibefradil on the conduction system were evaluated in 71 patients in a placebo-controlled trial. Mibefradil was administered IV at doses that produced plasma concentrations seen

POSICOR® (mibefradil dihydrochloride)

following oral administration of mibefradil at 50 mg and 100 mg. In this study, mibefradil slightly lengthened the corrected sinus node recovery time and AH interval and raised the Wenckebach point. Atrial effective and functional refractory periods, AV node functional and effective refractory periods and the conduction time in the His-Purkinje system and ventricular tissue were not affected.

Mibefradil causes dose-related flattening of the T wave and an increase in the voltage of the U wave. The U wave can sometimes become so large that it merges with the flattened T wave, and the resulting pattern has sometimes been misread (by both automated electrocardiographic interpreters and clinicians) as QTc prolongation.

The exact definition of this phenomenon is arbitrary. Changes sufficient to be misread as QTc prolongation in clinical trials did not occur at the therapeutic doses of 50 mg or 100 mg of mibefradil but were observed in 1% of patients who received 150 mg and 5.4% of patients who received 200 mg, both of which are above the recommended doses. Similar patterns have been seen in subjects treated with high and supratherapeutic doses of diltiazem and verapamil. The addition of POSICOR to chronic beta-blocker treatment was evaluated in both hypertensive and chronic stable angina pectoris patients (195 patients) and was associated with changes in heart rate and PR interval similar to those seen in patients treated with mibefradil alone. There were no cases of second- or third-degree AV block in these patients. In 44 angina patients treated with POSICOR and beta-blockers, no acute withdrawal effects, such as worsening of angina or palpitations, were seen upon beta-blocker discontinuation.

The combination of POSICOR and digoxin was not associated with an additional prolongation of PR time beyond the effect of POSICOR alone.

Effects in Hypertension: The antihypertensive effects of POSICOR were demonstrated in four placebo-controlled, double-blind, randomized trials conducted for 4 to 14 weeks, three in patients receiving no other treatment and one in patients still hypertensive while receiving 25 mg of hydrochlorothiazide. These involved 1123 patients with hypertension (933 on POSICOR and 190 on placebo). Once-daily administration of 50 mg and 100 mg was consistently associated with clinically and statistically significant reductions in both systolic and diastolic blood pressure. The mean differences from placebo in systolic/diastolic blood pressure at trough (24 hours post dose), for the 50 mg and 100 mg doses were about 7-11/5-7 and 7-10/9-11 mmHg, respectively. The antihypertensive effect of POSICOR was present in the sitting, standing and supine positions. The antihypertensive effect was not associated with reflex tachycardia, but rather a slight decrease in heart rate. The blood pressure was controlled over the 24-hour dosing interval, with little difference between trough and peak effect (trough to peak ratio >75%). A modest effect was seen on Day 1, and the full antihypertensive effect was reached within one to two weeks.

Long-term antihypertensive effects were demonstrated in two four-month, randomized, placebo-controlled withdrawal studies involving 221 patients on mibefradil. Blood pressure returned to approximately pretreatment levels in four weeks. Thus, there was no tolerance (loss of efficacy) observed on long-term administration. Additionally, no rebound increase in blood pressure was seen on discontinuation of POSICOR.

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The antihypertensive effects of POSICOR were similar regardless of race, gender, body weight, history of diabetes mellitus or history of coronary artery disease. POSICOR was effective in lowering high blood pressure in patients with chronic renal failure complicated by systemic hypertension. Additive antihypertensive effects have been observed in clinical trials where POSICOR was combined with diuretics, ACE inhibitors and beta-blockers.

Effects in Chronic Stable Angina Pectoris: The antianginal and antiischemic efficacy of POSICOR was demonstrated in five placebo-controlled, double-blind, randomized trials, involving 870 patients with chronic stable angina pectoris, 564 on POSICOR and 306 on placebo. Once-daily administration of 100 mg was associated with statistically significant increases in all exercise test parameters, in all studies, but the effect of 50 mg was smaller and less consistent. The increases in symptom-limited exercise duration at trough (24 hours post dose) for POSICOR 50 mg and 100 mg were about 20 seconds (seen in two of three studies) and about 50 seconds (in all three studies), respectively. In these studies, POSICOR also significantly delayed the time to onset of angina during exercise and, in a pooled analysis, decreased the rate of anginal attacks and nitroglycerin consumption reported by the patients. Additionally, POSICOR significantly delayed the onset of ischemia (persistent 1mm ST segment depression) during exercise in all placebo-controlled studies. These antianginal and antiischemic effects were associated with a dose-dependent mean decrease in double product for any given level of exercise (heart rate x systolic blood pressure), mainly due to a decrease in heart rate.

Long-term improvements in exercise test parameters were demonstrated in a four-month, randomized, placebo-controlled withdrawal study involving 102 patients on mibefradil. Thus, there was no tolerance (loss of efficacy) observed on long-term administration. Additionally, no rebound increase in anginal symptomatology was seen on discontinuation of POSICOR.

The antianginal effects of POSICOR were similar regardless of gender, race, body weight or history of hypertension, diabetes mellitus, myocardial infarction, PTCA or CABG. Improvements in all exercise test parameters and anginal symptomatology were observed in three placebo-controlled, double-blind, randomized clinical trials in which POSICOR was added to therapy with beta-blockers or long-acting nitrates.

INDICATIONS AND USAGE: *Hypertension:* POSICOR is indicated for the treatment of hypertension. POSICOR can be used alone or in combination with other antihypertensive agents.

Chronic Stable Angina Pectoris: POSICOR is indicated for the treatment of chronic stable angina pectoris. POSICOR can be used alone or in combination with other antianginal drugs.

CONTRAINDICATIONS: POSICOR is contraindicated in patients with:

1. Sick sinus syndrome or second- or third-degree AV block, without a pacemaker;
2. A known sensitivity to mibefradil;
3. Coadministration of terfenadine, astemizole and cisapride.

POSICOR® (mibefradil dihydrochloride)

WARNING: As described in the CLINICAL PHARMACOLOGY section, mibefradil may cause dose-related changes in the appearance of the electrocardiographic T and U waves. These changes may interfere with measurement of the QTc interval. Some drugs (eg, quinidine, sotalol) are sometimes monitored by following the QTc interval on serial electrocardiograms, in order to reduce the risk of torsades de pointes and other malignant arrhythmias. When mibefradil is coadministered with these drugs, it may be difficult to utilize serial electrocardiograms for this purpose.

PRECAUTIONS: *General:* POSICOR inhibits cytochrome P450 2D6 and 3A4 and can interact with many concomitant drugs, increasing their plasma concentrations (see *Drug Interactions*).

Hypotension: Although hypotension, postural hypotension, and syncope have been only rarely associated with POSICOR, and are not clearly more common than with placebo, caution should be exercised when administering POSICOR, particularly to patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Acute hemodynamic studies in a small number of patients with ischemic heart disease with or without impaired cardiac function treated with POSICOR have not demonstrated negative inotropic effects, nor was POSICOR associated with reflex tachycardia or an increase in neurohormones. Long-term studies in patients with moderate to severe (NYHA III, IV) heart failure have not been carried out. As with all calcium antagonists, caution should be exercised when treating patients with heart failure or compromised ventricular function.

Patients with Hepatic Failure: Since mibefradil is extensively metabolized by the liver, caution should be exercised when administering POSICOR to patients with severe hepatic impairment.

Cardiac Conduction: As described under CLINICAL PHARMACOLOGY, POSICOR slows sinus and AV node conduction, sometimes resulting in abnormally low heart rates; 0.7% and 1.4% of patients had heart rates below 45 bpm on 50 mg and 100 mg, respectively. Therefore, patients with a pretreatment heart rate below 50 bpm should be followed closely. Treatment with POSICOR has rarely been associated with second-degree AV block, 0.2% of patients on doses of 50 mg to 100 mg. No cases of third-degree AV block have been reported at 50 mg to 100 mg, but at higher doses third-degree AV block can rarely occur.

Drug Interactions: *Effects of Other Drugs on Mibefradil Pharmacokinetics:* No clinically relevant changes in pharmacokinetics of mibefradil have been seen in specific studies when mibefradil was coadministered with enalapril, atenolol, metoprolol, theophylline and cimetidine.

Effects of Mibefradil on the Pharmacokinetics of Other Drugs: **Interactions with Drugs Metabolized by Cytochrome P450 Enzymes:** In vitro results indicate that some isozymes of the cytochrome P450 enzyme system, including 2D6, 1A2, and 3A4, are inhibited in the presence of mibefradil or its metabolites. Coadministration of POSICOR with drugs metabolized by these isozymes may result in increased plasma concentrations of these drugs.

Drugs Metabolized by Cytochrome P450 2D6: A subset (about 7%) of the white population and 1% and 2% of Orientals and blacks, respectively, have reduced activity of the drug-metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase). Such individuals are

POSICOR® (mibefradil dihydrochloride)

referred to as "poor metabolizers" of such drugs as dextromethorphan, the type 1C antiarrhythmics propafenone, flecainamide and mexiletine, some beta-blockers and tricyclic antidepressants (particularly those with high first-pass effect, ie, desipramine and imipramine). Poor metabolizers have higher than expected plasma concentrations of such drugs when given in usual doses. Depending on the fraction of the drug metabolized by cytochrome P450 2D6, the increase in plasma concentration may be small or quite large. POSICOR, like several other drugs, inhibits the activity of this isozyme and can make previously normal metabolizers resemble poor metabolizers. Concomitant use of POSICOR with drugs metabolized by cytochrome P450 2D6 may require dose adjustment of the other drugs.

Tricyclic Antidepressants: Imipramine and desipramine have been shown to have substantial (seven- to eightfold) increases in AUC when CYP 450 2D6 metabolism is inhibited; concomitant use of tricyclic antidepressants with POSICOR would require substantial dose adjustment of the tricyclic antidepressant.

Drugs Metabolized by Cytochrome P450 3A4: POSICOR and/or its metabolites also inhibits the activity of cytochrome P450 3A4, an enzyme responsible for the metabolism of many drugs, including quinidine, short-acting benzodiazepines, most calcium-channel blockers, terfenadine astemizole and cisapride. POSICOR may increase plasma concentrations of coadministered drugs that are primarily metabolized by the cytochrome P450 3A4 enzyme system and may consequently increase or prolong their therapeutic and adverse effects. Therefore, unless otherwise specified, dosage adjustment of these drugs may be necessary. For drugs that can cause serious adverse effects if concentration is increased, concomitant use with POSICOR should be avoided (see CONTRAINDICATIONS).

The following drug interactions have been identified involving mibefradil and other drugs metabolized by the cytochrome P450 system:

Terfenadine: Coadministration of terfenadine (metabolized by CYP 450 3A4) with POSICOR in healthy subjects led to elevated plasma concentrations of terfenadine up to 40 ng/mL with twice-daily dosing of 60 mg terfenadine, resulting in a 12% increase in mean QTc interval. Since QTc prolongation due to elevated plasma concentrations of terfenadine can be associated with life-threatening cardiac dysrhythmias and death, coadministration of POSICOR with terfenadine is contraindicated (see CONTRAINDICATIONS).

Astemizole and Cisapride: Although there are no specific studies of interaction of mibefradil with these drugs, substantial inhibition of their metabolism would be expected. Since elevated plasma concentrations of astemizole and cisapride can be associated with life-threatening cardiac dysrhythmias, their use with mibefradil is contraindicated. One such case has been observed in a patient receiving cisapride and concomitant mibefradil.

Cyclosporine A: Cyclosporine A (Sandimmune®), a drug metabolized by CYP 450 3A4, levels increased about twofold under concomitant treatment with 50 mg POSICOR for eight days. Therefore, cyclosporine A levels should be monitored and its dose adjusted accordingly.

POSICOR® (mibefradil dihydrochloride)

Quinidine: In healthy volunteers, elevations in peak quinidine plasma concentrations (15% to 19%) and AUC (50%) were found during coadministration of single doses of quinidine with POSICOR 50 mg and 100 mg, but the active metabolite of quinidine was markedly reduced. No clinically relevant pharmacodynamic interactions were observed.

Metoprolol: Coadministration of POSICOR with metoprolol (metabolized by CYP 450 2D6) in healthy subjects resulted in a twofold increase in peak plasma concentrations of total (R- and S-enantiomeric) metoprolol and about four- to fivefold increase in AUC. Elimination half-life increased from three hours to seven to eight hours. The increase in the pharmacologically more active S-isomer, however, is only about 30%, so that little pharmacologic effect or effect on cardioselectivity would be expected with concomitant POSICOR.

Other Information: In clinical studies, POSICOR has been administered without apparent harm with commonly used drugs including diuretics, beta-blockers, ACE inhibitors, nonsteroidal antiinflammatory drugs, long-acting nitrates, sublingual nitroglycerin, oral hypoglycemics, fibrate lipid-lowering agents, conjugated estrogens, antibiotics and antithrombotics. CYP 450 3A4 mediates the metabolism of several HMG CoA reductase inhibitors. Use of these drugs has been associated with rhabdomyolysis, which may be more frequent when they are coadministered with drugs that inhibit CYP 450 3A4. Although ~~However,~~ no such adverse interaction has been seen with POSICOR, the possibility should be considered.

Specific Interaction Studies: In specific studies, no clinically relevant interactions have been observed between the recommended doses of POSICOR and enalapril, atenolol or cimetidine. Despite in vitro evidence of inhibition of CYP 450 1A2, no pharmacokinetic interaction was observed with theophylline, a CYP 450 1A2 substrate. In healthy volunteers, small elevations in digoxin peak plasma levels (20% to 30%) were found during coadministration with POSICOR 50 mg and 100 mg, but trough plasma levels were unchanged in these volunteers and in patients with congestive heart failure.

Protein Binding: Mibefradil is highly protein bound (99.5%), mainly to alpha$_1$-acid glycoprotein (95%). Therefore, it will not displace drugs which bind to serum albumin, such as warfarin, phenytoin and digoxin.

Information for Patients: Patients should be instructed to take POSICOR whole and not to crush or chew the tablet. Patients should inform their physicians if they are pregnant or plan to become pregnant or are breastfeeding. Patients should be informed that lightheadedness or fatigue can occur and that these symptoms should be reported to a physician.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Mibefradil was not mutagenic in the Ames microbial mutagenicity test with or without metabolic activation, in the microbial test with E. coli or in Chinese hamster V79 cells. No genotoxicity was observed in a test of unscheduled DNA synthesis in rat primary hepatocytes, and no chromosomal damage was observed in a test of human peripheral blood lymphocytes treated in vitro or in an in vivo micronucleus test.

A decrease in mating incidence and a prolongation of time to mating was observed when male and female rats were treated with mibefradil dihydrochloride at a daily dose of 39 mg mibefradil/kg

POSICOR® (mibefradil dihydrochloride)

(approximately three times the maximum recommended human dose [MRHD] on a mg/m^2 basis) prior to and during the mating period. For those females successfully mated at this dose, there was a decrease in fetuses/dam observed at caesarean section or pups/dam at natural delivery, findings associated with both a decrease in number of corpora lutea per dam (evidence of a decrease in ovulation) and an increase in preimplantation loss (ovulations not resulting in implants).

Oral gavage administration of mibefradil dihydrochloride to male mice for up to 95 weeks and to female mice for up to 104 weeks at doses up to 65 mg mibefradil/kg/day (about three times the MRHD of 100 mg mibefradil/day on a mg/m^2 basis) revealed no evidence of a carcinogenic effect of mibefradil. When administered in the feed of rats at doses of 35 mg mibefradil/kg/day (about three times the MRHD on a mg/m^2 basis) for up to 104 weeks, an increased incidence of squamous cell carcinoma of the oral cavity was observed. A similar association was observed when another rat study was conducted with similar doses of mibefradil administered by gavage. The latter study, which evaluated diet as a risk factor for the oral cavity tumors, demonstrated that the carcinogenic effect of mibefradil was dependent on the aggressiveness (in terms of producing severe periodontitis) of the diet employed combined with class-related gingival overgrowth. No tumors were observed when mibefradil was administered to rats fed a less aggressive diet associated with much lower levels of periodontitis.

Pregnancy: Pregnancy Category C. Developmental toxicity studies have been conducted in rats and rabbits. In rabbits, no adverse effects on development were seen with doses up to 35 mg mibefradil/kg/day (approximately seven times the MRHD on a mg/m^2 basis). In rats there was an increased incidence of fetuses with cardiovascular abnormalities at 39 mg/kg/day (approximately three times the MRHD). Skeletal and visceral defects have been observed following the administration of other calcium antagonists to pregnant rodents or rabbits. There are no adequate and well-controlled studies in pregnant women. POSICOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: Dystocia and/or prolongation of pregnancy, which was associated with uterine prolapse, stillbirths and neonatal mortality, was observed to occur when mibefradil dihydrochloride was administered to pregnant rats, during the expected time of parturition, at 13 or more mg mibefradil/kg/day (13 mg/kg/day is approximately equal to the MRHD on a mg/m^2 basis). Calcium-channel blocking agents have been shown to inhibit uterine contraction in rats, rabbits and humans, presumably by inhibition of Ca^{++} influx in the myometrium. POSICOR should be avoided during the time of expected labor and during parturition.

Nursing Mothers: When mibefradil was administered to lactating rats, their milk attained mibefradil concentrations two to five times greater than those in their serum. If mibefradil enters human milk in similar quantities, then a human infant ingesting such milk would (scaling directly by weight) be expected to develop serum mibefradil levels somewhat less than those of the mother. On the other hand, mibefradil levels have not been measured in human milk. The pharmacokinetics and pharmacodynamics of mibefradil in human infants have not been studied, and neonates have been reported to be disproportionately sensitive to some other calcium-channel blockers. Administration of mibefradil should therefore be avoided, if possible, in lactating women who continue to nurse.

POSICOR® (mibefradil dihydrochloride)

Pediatric Use: Safety and effectiveness of POSICOR in pediatric patients have not been established.

ADVERSE REACTIONS: POSICOR has been evaluated for safety in 3430 patients (2194 with hypertension, 1236 with chronic stable angina pectoris). In general, treatment with POSICOR was well tolerated at doses up to 100 mg daily. Most adverse reactions associated with POSICOR were transient and of mild or moderate intensity. In placebo-controlled clinical trials, the rate of discontinuation of POSICOR (50 mg and 100 mg) due to adverse reactions was similar to that of placebo. Discontinuation due to dizziness was the only reason for premature withdrawal that ~~which~~ was more common on mibefradil than on placebo. In the pooled placebo-controlled trials that studied doses of 50 mg/day and 100 mg/day, the incidence of adverse experiences present in at least 1% of patients treated with the 100 mg dose and more common on that dose than on placebo were: hypotension cardiac angina

	Placebo	POSICOR	
		50 mg	100 mg
	(N=283)	(N=279)	(N=285)
Headache	6%	3%	8%
Leg Edema	3%	1%	4%
Rhinitis	0%	3%	3%
Abdominal Pain	1%	1%	2%
Light-Headed Feeling	0%	1%	3%
Dyspepsia	1%	1%	2%

The following adverse experiences were also present in >1% of patients treated with the 100 mg dose but occurred at a frequency equal to or less than placebo: allergic reaction, angina pectoris, dizziness, fatigue, flushing, influenza, palpitations, upper respiratory tract infection and vomiting/nausea.

The following adverse experiences occurred in a dose-related manner in placebo-controlled trials over a dose range of 50 mg to 150 mg: dizziness, dyspepsia, flushing, leg edema, rhinitis and vomiting/nausea.

There were no clinically important differences in the effect of POSICOR on adverse experience rates based on age, gender or race.

In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, the following adverse experiences, whether drug related or not, occurred at a frequency greater than 0.5% or occurred at a lower rate but were potentially important:

Autonomic Nervous System: increased sweating, orthostatic complaints, postural hypotension, syncope

Body as a Whole: generalized weakness, trauma

Cardiovascular: bradycardia, chest pain nonspecific, hypotension ~~coronary artery disorders~~ cardiac failure

Immunologic: angioedema

HLR Posicor 6/18/97

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Central and Peripheral Nervous System: paresthesia

Gastrointestinal: constipation, diarrhea, flatulence, gastroenteritis ~~tooth disorder~~, rectal hemorrhage

Hearing and Vestibular: ear buzzing, otitis

Musculoskeletal: arthritis, back pain, chest pain, muscle cramps, pain of extremities, sprains and strains

Psychiatric: anxiety, depression, insomnia ~~psychic disorder~~

Reproductive, Male: impotence

Respiratory: bronchitis, coughing, dyspnea, nasal congestion, pharyngitis, sinusitis

Skin and Appendages: rash, exfoliative dermatitis

Urinary System: urinary tract infection

Vision: conjunctivitis

Electrocardiographic Changes: Treatment emergent ECG changes that clearly occurred in a dose-related manner in the placebo-controlled trials were bradycardia (heart rate < 45 bpm): 0.7% (50 mg) and 1.4% (100 mg) and first-degree AV block: 3.6% (50 mg) and 8.4% (100 mg). In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, second-degree AV block was recorded in 0.2% of the patients.

POSICOR therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in hematology parameters, serum potassium, sodium, calcium, glucose, plasma lipids, uric acid, urea nitrogen, creatinine or liver function tests.

OVERDOSAGE: At present there has been no experience with single doses >350 mg or multiple doses >250 mg. Doses higher than these might cause excessive peripheral vasodilation with marked hypotension, bradycardia and/or high-degree AV block. If a patient is suspected of having taken an overdose, continuous ECG monitoring and repeated blood pressure measurements should be instituted. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium antagonists. As mibefradil is highly bound to plasma proteins, it cannot be removed by dialysis.

Bradycardia and high-degree AV block may be treated with atropine, isoproterenol and cardiac pacing.

DOSAGE AND ADMINISTRATION: The recommended doses of POSICOR are 50 mg and 100 mg once daily. The larger dose is, on average, more effective. Doses above 100 mg offer little or no

POSICOR® (mibefradil dihydrochloride)

additional benefit and induce a greater rate of adverse reactions. POSICOR can be taken with or without food. Tablets should be swallowed and not chewed or crushed.

Hypertension: The recommended initial dose of POSICOR is 50 mg once daily. Titration to 100 mg once daily should be based on blood pressure response; the full effect of a given dose level is generally seen after one to two weeks. The same dosage recommendations apply for all populations, including elderly patients and patients with chronic renal failure. However, caution should be exercised in patients with severe hepatic impairment.

Chronic Stable Angina Pectoris: The recommended initial dose of POSICOR is 50 mg once daily. Titration to 100 mg once daily should be based on therapeutic response. The same dosage recommendations apply for all populations, including elderly patients and patients with chronic renal failure. However, caution should be exercised in patients with severe hepatic impairment.

Coadministration with Other Antihypertensive and/or Antianginal Drugs: POSICOR has been safely administered with diuretics, ACE inhibitors, beta-blockers, long-acting nitrates and sublingual nitroglycerin.

Administration in Subpopulations: POSICOR has been used safely in patients regardless of demographic factors (age, race, gender, body weight) and common concomitant diseases, such as chronic renal failure, chronic obstructive pulmonary disease and diabetes mellitus.

HOW SUPPLIED: POSICOR is supplied as biconvex, hexagonal tablets, available in bottles and Tel-E-Dose® packages as follows:

	50 mg	100 mg
color	pale yellow	light orange
engraving	ROCHE POSICOR 50	ROCHE POSICOR 100
bottle of 100	NDC 0004-0080-01	NDC 0004-0081-01
bottle of 300	NDC 0004-0080-27	---
Tel-E-Dose® of 100	NDC 0004-0080-49	NDC 0004-0081-49

Storage Conditions: Store at 15° to 30°C (59° to 86°F) in tight containers as defined in USP/NF.

POSICOR® (mibefradil dihydrochloride)

(Roche Hexagon)

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

25995005-0697

Issued: June 1997
Printed in USA

Exhibit (3)

United States Patent [19]

Branca et al.

[11] **Patent Number: 4,808,605**

[45] **Date of Patent: Feb. 28, 1989**

[54] **TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS**

[75] Inventors: **Quirico Branca; Roland Jaunin; Hans P. Märki**, all of Basel; Fränzi Marti, Riehen; **Henri Ramuz**, Birsfelden, all of Switzerland

[73] Assignee: **Hoffmann-La Roche Inc.**, Nutley, N.J.

[21] Appl. No.: **119,114**

[22] Filed: **Nov. 10, 1987**

[30] **Foreign Application Priority Data**

Nov. 14, 1986 [CH] Switzerland 4565/86

[51] **Int. Cl.**[4] **A61K 31/415**; C07D 413/06

[52] **U.S. Cl.** **514/394**; 514/220; 514/221; 514/234.5; 514/303; 514/338; 514/367; 514/373; 514/387; 514/395; 514/400; 540/496; 540/506; 540/507; 544/139; 546/118; 546/271; 548/161; 548/179; 548/180; 548/305; 548/329; 548/330; 548/342

[58] **Field of Search** 514/220, 221, 300, 367, 514/373, 394, 234.5, 303, 338, 387, 395, 400; 540/496, 506, 507; 546/118, 271; 548/160, 329, 330, 161, 179, 180, 305, 342; 544/139

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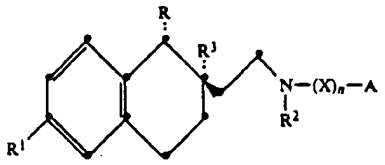
Primary Examiner—Richard A. Schwartz

Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; Matthew Boxer

[57] **ABSTRACT**

Compounds of the formula



I

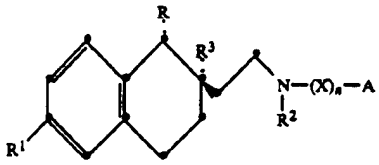
wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1-C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alkyl-carbonyloxy, lower-alkoxy-lower-alkylcarbonoyloxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower alkylaminocarbonyloxy, X is C_1-C_{18}-alkylene which optionally can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrolo[2,1-c]-[1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof. The compounds of formual I have a pronounced calcium-antagonistic and anti-arrhythmic activity and can accordingly be used as medicaments, especially for the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

21 Claims, No Drawings

TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS

BRIEF SUMMARY OF THE INVENTION

The invention relates to tetrahydronaphthalene derivatives of the formula



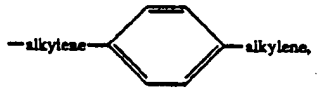
I

wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1–C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower-alkylaminocarbonyloxy, X is C_1–C_{18}-alkylene, C_1–C_{18}-alkylene which is interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]-pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof.

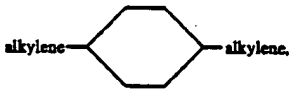
The compounds of formula I are useful as agents for the treatment or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "lower-alkyl"—alone or in combination—denotes straight-chain and branched, saturated hydrocarbon groups with 1–6, preferably 1–4, carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl and the like. The term "C_1–C_{12}-alkyl" denotes straight-chain and branched, saturated hydrocarbon groups with 1–12 carbon atoms. The term "lower-alkoxy" denotes lower-alkyl ether groups in which the term "lower-alkyl" is as described above. The term "halogen" denotes the four halogen atoms fluorine, chlorine, bromine and iodine. The term "C_1–C_{18}-alkylene" denotes straight-chain or branched-saturated hydrocarbon groups with 1–18 carbon atoms such as methylene, ethylene, propylene, methylethylene, butylene, 1,1-dimethylpropylene, pentamethylene, 1-methylpentamethylene, hexamethylene, heptamethylene, undecamethylene and the like. The term "aryl" denotes phenyl optionally mono- or multiply-substituted by halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, nitro or amino. The term "aryl-lower-alkyl" denotes straight-chain or branched lower-alkyl groups in which one or more hydrogen atoms is/are replaced by aryl groups, such as benzyl, phenethyl and the like. Examples of optionally substituted benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl or pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl are 2-benzimidazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 3-methylbenzimidazolonyl, 3-isopropylbenzimidazolonyl, 3-butylbenzimidazolonyl, 3-morpholinoethylbenzimidazolonyl, 3-benzylbenzimidazolonyl, 2-pyridylmethylbenzimidazolonyl, 2-imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, 2-benzthiazolyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl, 5,6-dimethyl-2-benzimidazolyl and the 106 like. Examples of di- and tri-substituted 2-imidazolyl attached via an ethylene group are 1-methyl-4,5-diphenyl-2-imidazolylethyl and 4,5-diphenyl-2-imidazolylethyl and the like. The term "leaving group" denotes conventional leaving groups such as halogen, preferably chlorine or bromine, arylsulphonyloxy such as, for example, tosyloxy, bromobenzenesulphonyloxy, benzenesulphonyloxy or mesitylenesulphonyloxy, or alkylsulphonyloxy such as, for example, mesyloxy or trifluoromethylsulphonyloxy. The term "N-oxide" denotes a compound wherein the nitrogen which is oxidized is the nitrogen which is attached via an ethylene to the tetrahydronaphthalene moiety. The terminology that X is C_1–C_{18} alkylene which can be interrupted by 1,4-phenylene denotes that the moiety, X, can be



wherein the total number of carbon atoms in the two alkylene moieties together is not greater than 18. The terminology that X is C_1–C_{18} alkylene which can be interrupted or lengthened by 1,4-cyclohexylene denotes that the moiety, X, can be

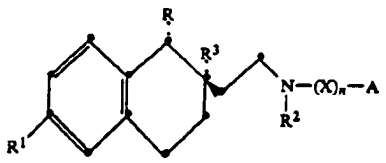


or that X can be an alkylene moiety with cyclohexylene attached either to the A moiety or the

moiety.

The term "pharmaceutically usable acid addition salt" denotes salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like. Such salts can be manufactured readily by any person skilled in the art having regard to the state of the art and taking into consideration the nature of the compound to be converted into a salt.

The invention relates to tetrahydronaphthalene derivatives of the formula



wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1–C_{12}-alkyl, R^3 hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower-alkylaminocarbonyloxy, X is C_1–C_{18}-alkylene, C_1–C_{18}-alkylene which is interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group or benzimidazolyl, substituted benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl or pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof.

The compounds of formula I are useful as calcium antagonists. More specifically, the compounds of formula I are useful as agents in the treatment or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

Those compounds of formula I in which R is isopropyl are preferred. R^3 preferably is hydroxy, lower-alkylcarbonyloxy, particularly isobutyryloxy, lower-alkoxy-lower-alkylcarbonyloxy, particularly methoxyacetyloxy, or lower-alkylaminocarbonyloxy, particularly butylaminocarbonyloxy. n preferably is the number 1. Further, those compounds of formula I in which R^1 is fluorine are preferred. Those compounds of formula I in which R^2 is methyl are also preferred. The compounds of formula I in which X is C_3–C_7-alkylene, particularly propylene, butylene, pentamethylene or hexamethylene, are likewise preferred. A preferably signifies 2-benzimidazolyl, 2-benzthiazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydro-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl or 1-methyl-4,5-diphenyl-2-imidazolyl, particularly 2-benzimidazolyl or 2-benzthiazolyl.

More, preferred are those compounds of formula I in which R is isopropyl, R^3 is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy. R^1 is fluorine, R^2 is methyl, X is propylene, butylene, pentamethylene or hexamethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

Especially preferred compounds of formula I are:

2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate; and

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate.

Exemplary of other compounds of formula 1 are:

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-1-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl butylcarbamate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(2-oxo-1-benzimidazolinyl)hexyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methyl-N-oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(1-dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(2-benzimidazolyl)methyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzimidazoly)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate; [1S,2S]-2-[2-[[4-(2-benzimidazoly)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]-dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthalenol;

[1S,2S]-2-[2-[[4-(2-Benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]-dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]-ethyl-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxynaphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthalenol;

[1S,2S]-2-[2-[[7-(1-dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[(2-benzthiazolyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

1-[2-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]ethyl]-2-benzimidazolinone;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[2-(2-oxo-1-benzimidazolinyl)ethyl]amino]ethyl]-2-naphthyl methoxyacetate;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-methyl-2-benzimidazolinone;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthalenol;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazoline;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-isopropropyl-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-butyl-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-(2-morpholinoethyl)-2-benzimidazolinone;

1-benzyl-3-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone;

3-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(2-oxo-1-benzimidazolinyl)butyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[6-(1,2-dihydro-2-oxo-3H-imidazo[4,5-c]-pyridin-3-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-methyl-2-oxo-1-benzimidazolinyl)hexyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(3-isopropyl-2-oxo-1-benzimidazolinyl)-butyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-butyl-2-oxo-1-benzimidazolinyl)hexyl-]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-[3-(2-morpholinoethyl)-2-oxo-1-benzimidazolinyl]hexyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[4-(3-benzyl-2-oxo-1-benzimidazolinyl)-butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-[2-oxo-3-(2-pyridylmethyl)-1-benzimidazolinyl]butyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl isobutyrate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl carbanilate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl benzylcarbamate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl p-chlorocarbanilate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(1-methyl-2-benzimidazolyl)methyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[1-(1-methyl-2-benzimidazolyl)ethyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[trans-4-(2-benzimidazolyl)cyclohexyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2,5(1H)-dione;

(S)-6-chloro-10-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]-methylamino]butyl]-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-(10H)-dione;

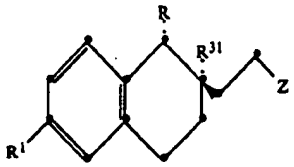
[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-ben-

zodiazepin-1-yl)butyl]methylamino]ethyl]-2-naphthyl methoxyacetate; and

[1S,2S]-2-[2-[[4-[(S)-6-chloro-2,3,11,11a-tetrahydro-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate.

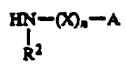
The compounds of formula I in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof can be prepared as follows:

(a) for the making of compounds of formula I in which R^3 is hydroxy or lower-alkoxy and R, R^1, R^2, A, X and n are as described above, reacting a compound of the formula



II

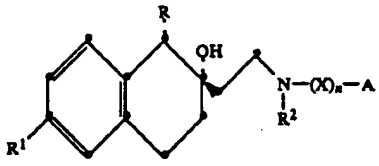
wherein R^{31} is hydroxy or lower-alkoxy and Z is a leaving group and R and R^1 are as described above, with an amine of the formula



III

wherein R^2, A, X and n are as described above, or

(b) for the making of compounds of formula I in which R^3 is lower-alkylcarbonyloxy or lower-alkoxy-lower-alkylcarbonyloxy and R, R^1, R^2, A, X and n are as described above reacting a compound of the formula



Ia

wherein R, R^1, R^2,A, X and n are as described above, with an acylating agent yielding a lower-alkylcarbonyl or lower-alkoxy-lower-alkylcarbonyl group, or

(c) for the making of compounds of formula I in which R^3 is lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower-alkylaminocarbonyloxy and R, R^1, R^2, A, X and n are as described above, reacting a compound of formula Ia above with a lower-alkyl, aryl or aryl-lower-alkyl isocyanate, and, if desired,

(d) oxidizing a compound obtained to the corresponding N-oxide, and/or

(e) separating a racemate obtained into the optical antipodes, and/or

(f) converting a compound obtained into a pharmaceutically usable acid addition salt.

A compound of formula II is reacted with an amine of formula III according to conventional methods. The reaction is carried out in the presence or absence of an organic solvent which is inert under the reaction conditions at a temperature between about 20° and 150° C., preferably between about 80° and 120° C. Solvents such as dimethylformamide, dimethyl sulphoxide, alcohols such as isopropanol or tert.-butanol, ethers such as tetrahydrofuran or dioxan, aromatic hydrocarbons such as benzene, toluene or xylene, chlorinated hydrocarbons such as methylene chloride, carbon tetrachloride or chlorobenzene, and the like come into consideration in this reaction. The reaction is advantageously carried out in the presence of an acid-binding agent, for example a tertiary amine such as trimethylamine, triethylamine, ethyldiisopropylamine or 1,5-diazabicyclo[4.3.0]-non-5-ene, whereby excess amine of formula III can also serve as the acid-binding agent. For reasons of convenience the reaction is carried out at atmospheric pressure, although higher pressure can also be used.

The acylation of a compound of formula Ia is also carried out according to conventional methods. Suitable acylating agents are, in particular, activated acid derivatives such as acid halides and acid anhydrides or mixed acid anhydrides. The reaction is carried out in an organic solvent or solvent mixture which is inert under the reaction conditions at a temperature between about 0° C. and the reflux temperature. As solvents there come into consideration, in particular, aromatic hydrocarbons such as benzene, toluene or xylene, chlorinated hydrocarbons such as methylene chloride or chloroform, ethers such as diethyl ether, tetrahydrofuran or dioxan, and the like.

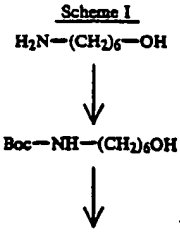
The reaction of a compound of formula Ia with an isocyanate can also be effected according to conventional methods in an organic solvent or solvent mixture which is inert under the reaction conditions at a temperature between about 50° C. and the boiling point of the solvent or solvent mixture, preferably between about 80° and 120° C., in the presence of a catalyst such as a tin-(II) salt, e.g. tin-(II) 2-ethylhexanoate. As solvents there come into consideration, in particular, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as tetrahydrofuran or dioxan, and the like.

A compound obtained can be converted into the corresponding N-oxide likewise in a conventional manner by means of an oxidation agent such as hydrogen peroxide or a peracid such as peracetic acid or perbenzoic acidiin a solvent such as an alkanol, e.g. methanol or ethanol, and the like at a temperature between about 0° and 50° C., preferably at room temperature.

The starting materials of formulae II and III are known or can be obtained in accordance with known methods. A process for the preparation of a compound of formula III in which A is a heterocycle attached via a nitrogen atom or a carbon atom or di- or tri-substituted 2-imidazolyl attached via an ethylne group is outlined in Schemes I-III hereinafter in which Boc denotes tert.butoxycarbonyl, Bz denotes benzyl and Ph denotes phenyl. With respect to the precise reaction conditions, reference is made to the experimental section.

The starting materials of formula IV, XI and XV in Schemes I-III are known.

Scheme I

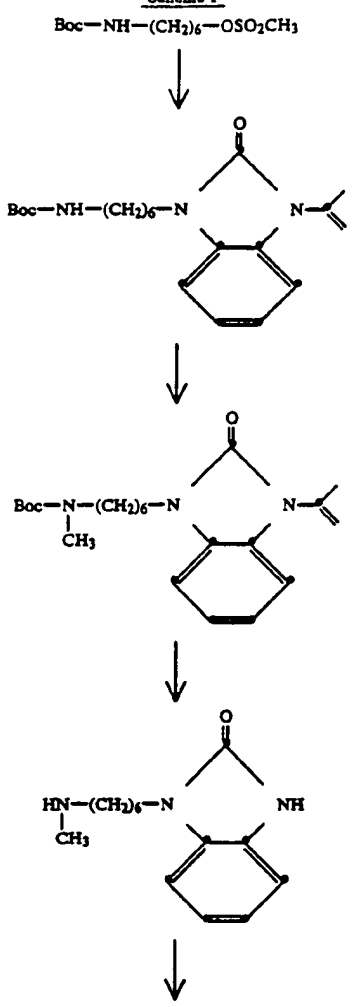


IV

V

-continued

Scheme I



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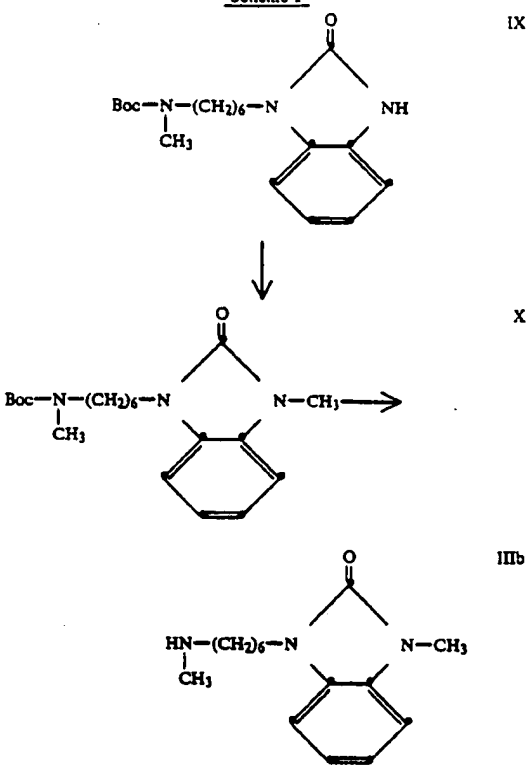
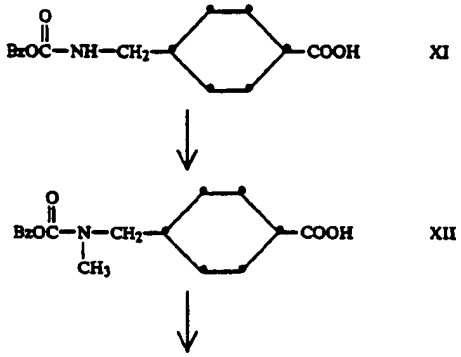
Scheme I



Scheme II



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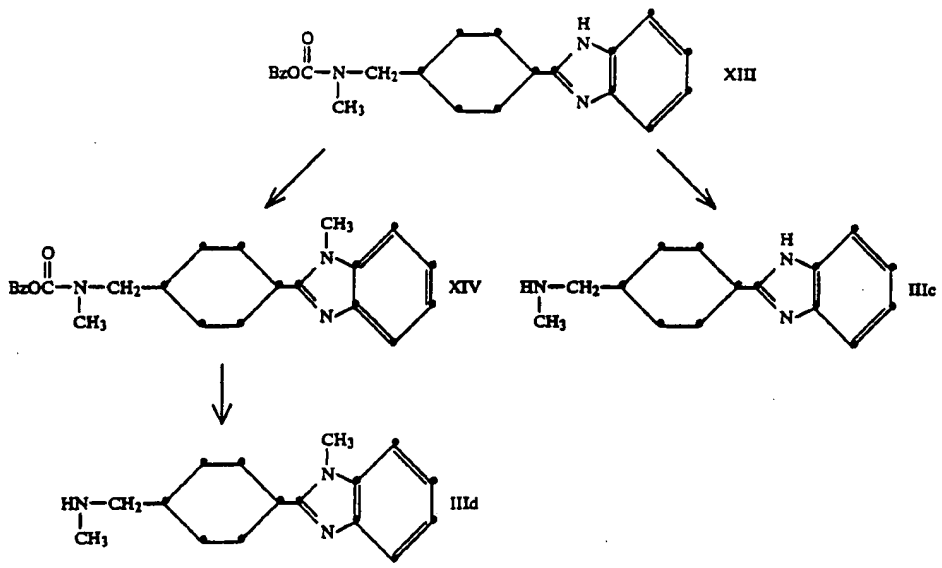
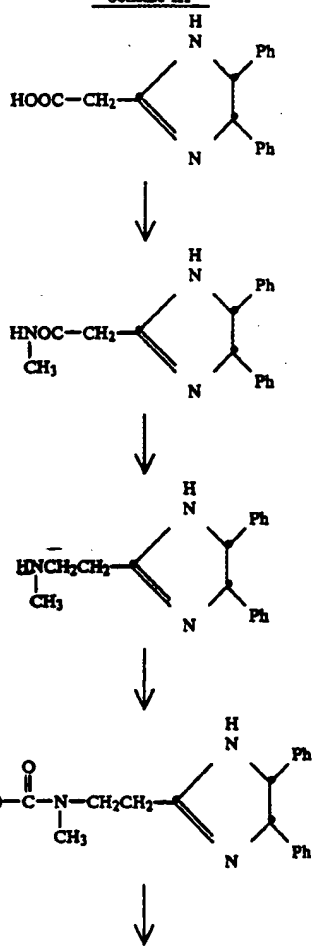
Scheme II



Scheme III



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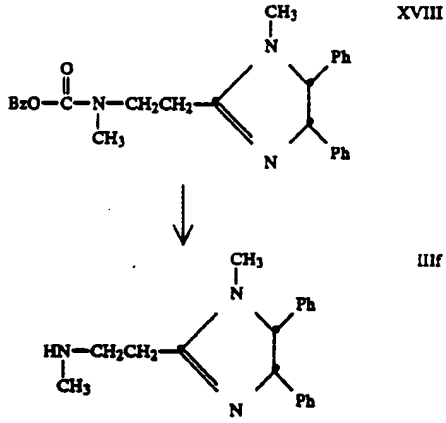
Scheme III



The compounds of formula I contain at least one asymmetric centre (2-position) and can therefore exist as optical antipodes or as racemates. Compounds of formula I which contain more than one asymmetric centre are present in the relative configuration indicated by formula I. The racemates of formula I can be resolved into the optical antipodes according to conventional methods, e.g. by reaction with an optically active acid and fractional crystallization of the salt obtained.

The compounds of formula I are characterized by valuable pharmacodynamic properties. In particular, the compounds of formula I have a pronounced calcium-antagonistic activity and can accordingly be used as medicaments, especially for the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

The calcium-antagonistic activity as well as the blood pressure-lowering properties of the compounds in accordance with the invention can be demonstrated in the tests described hereinafter:

A. ^{3}H-Desmethoxyverapamil binding determinations:

The determination is carried out on partially-cleaned membranes of guinea pig heart. The reaction mixture (0.3 ml) consists of 0.2–0.8 mg of membrane protein, 2.5 nM of ^{3}H-desmethoxyverapamil and various concentrations of test substances. The incubation lasts 120 minutes at 37° C. and is stopped by dilution with the incubation buffer; a filtration is subsequently carried out. The filter-bound radioactivity is measured with a scintillation counter. Specific binding (i.e. receptor-bound) is defined as the difference between total and unspecific-bound radioactivity. The unspecific binding is determined in the presence of an excess of non-radioactive verapamil (10 μM).

The activity (potency) of a compound in this test is defined by the IC_{50} value. The IC_{50} is the substance concentration (in mol/l) which produces a half-maximum inhibition of the specific ^{3}H-desmethoxyverapamil binding. This value is extrapolated from a concentration-binding curve.

B. Isolated, perfused guinea pig heart according to Langendorff:

Guinea pigs weighing approximately 400 g are narcotized with Urethan (1 g/kg i.p.) and the heart is removed rapidly. The aorta is cannulated and the heart is perfused retrogradely with a modified Krebs-Henseleit solution of the following composition in mM: NaCl 114.7, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5 and glucose 11.1. The solution is gassed with Oxycarbon (a mixture of 95% oxygen and 5% carbon dioxide) at pH 7.3 and a temperature of 37° C. The perfusion pressure is held constant at a value of 90 cm H_2O (8.83 kpa). A Miller microtip catheter pressure transducer (PC-350) is inserted in the left heart chamber in order to measure the left ventricular pressure. The total coronary artery flow is collected in a funnel and measured with an electro magnetic flow meter. All measurement parameters are recorded on a recording apparatus (Gould, Model 2800). The test begins after an adaptation of 45 minutes. Substances are infused with a velocity of 1% of the total coronary flow rate. A complete concentration-activity curve (10^{-10} to 10^{-6}M) is prepared for each substance. The two most important measurement parameters are: (1) CBF: coronary blood flow (in ml/min)—the velocity of blood flow through the coronary arteries and (2) dp/dt: rate of increase in left ventricular pressure (in mmHg/sec), as a measurement of the contractility force of the heart; this value is given as the % maximal variation from the initial value (Δ %) per dosage administered.

C. Haemodynamic parameters in the narcotized dog:

The 4 most important measurement parameters (with the respective measurement units) of the haemodynamic experiment are: (1) CBF: coronary blood flow (in ml/min)—the velocity of blood flow through the coronary arteries; (2) HR: heart rate (in beats/min)—the heart frequency; (3) BP: blood pressure (in mm Hg)—the blood pressure; and (4) dp/dt: rate of increase in left ventricular pressure (in mm Hg/sec) as a measurement of the contractility force of the heart. The values are given as the % maximum variation from the initial value (Δ %) and the duration of this variation (t) per dosage administered.

There is thus obtained not only an overall picture of the activity of the substance, but also an estimation as to the potential selectivity for a specific part of the circulatory system in the entire organism. After the administration of an anaesthetic, the dog is intubated and respired artificially. Blood pH, pC_2O , pO_2 and haemoglobin are measured hourly with a blood-gas analyser. The blood pressure (systolic and diastolic) is measured with a probe in the aorta abdominalis. The heart freguency is recorded by means of a tachometer, which is disengaged from the pressure pulse. For the other measurements the heart must be firstly be opened in order that a probe can be inserted in the left ventricle (heart chamber) for the pressure measurements (dp/dt). The coronary blood flow is measured with a flowing probe in the left coronary artery (descendens).

The results obtained in these tests are compiled in the following Table:

TABLE

	A	B		C				
		CBF						
Compound	IC_{50} [M]	IC_{50} [M]	dp/dt Δ %	CBF Δ %	HR Δ %	BP Δ %	dp/dt Δ %	Dosage mg/kg i.v.
A	$1.3 \cdot 10^{-7}$	$4.7 \cdot 10^{-8}$	250	86	−7	−22	25	0.3
B	$6.3 \cdot 10^{-7}$	$5.0 \cdot 10^{-8}$	216	36	0	−6	8	0.3
C	$2.1 \cdot 10^{-7}$	$1.7 \cdot 10^{-8}$	192	62	−9	−16	15	0.3
D	$3.2 \cdot 10^{-8}$	$1.1 \cdot 10^{-9}$	162	22	−25	−21	6	0.03
E	$1.0 \cdot 10^{-6}$	$1.0 \cdot 10^{-5}$	164	57	0	−8	10	1
F	$3.4 \cdot 10^{-8}$	$2.8 \cdot 10^{-8}$	130	46	−2	−3	4	0.3
G	$1.5 \cdot 10^{-7}$	$1.8 \cdot 10^{-9}$	237	96	−15	−20	11	0.3
H	$2.8 \cdot 10^{-8}$	$2.4 \cdot 10^{-9}$	222	146	−41	−28	25	0.3
I	$1.0 \cdot 10^{-7}$	$2.2 \cdot 10^{-8}$	124	82	−9	−14	18	0.3

A = [1S,2S]—2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate

B = [1S,2S]—2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol

C = [1S,2S]—6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl butylcarbamate

D = [1S,2S]—6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(2-oxo-1-benzimidazolinyl)hexyl-]amino]-ethyl]-2-naphthyl methoxyacetate

E = [1S,2S]—2-[2-[[3-(2-Benzimidazolyl)propyl]methyl-N—oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate

F = [1S,2S]—2-[2-[[7-(1-Dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate

G = [1S,2S]—2-6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]methyl-amino]ethyl]-2-naphthyl methoxyacetate

H = [1S,2S]—2-[2-[[5-(2-Benzthiazolyl)pentyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate

I = [1S,2S]—6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(2-benzimidazolyl)methyl[benzyl]methylamino]-ethyl]-2-naphthyl methoxyacetate

In the Table above, the IC_{50} of compound A in Test A is given as $1.3 \cdot 10^{-7}$. This means 1.3×10^{-7}. All other numbers which are similarly written have corresponding meanings. Thus $4.7 \cdot 10^{-8}$ means 4.7×10^{-8}.

The compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be carried out rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

For the manufacture of tablets, coated tablets, dragees and hard gelatine capsules the compounds of formula I can be processed with pharmaceutically inert excipients. A pharmaceutically inert excipient includes inorganic or organic excipients or mixtures thereof. For tablets, dragees and hard gelatine capsules, excipients such as lactose, maize starch or derivatives thereof, talc, stearic acid or its salts etc. may be used.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerine, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

The invention also relates to pharmaceutical compositions for the treatment or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency which comprise a compound of formula I and a pharmaceutically inert, inorganic or organic excipient.

The invention also relates to a method for treating or preventing angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency which comprises administering an effective amount of a compound of formula I to a warm-blooded animal in need of such treatment.

In accordance with the invention compounds of formula I can be used in the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency by administering an effective amount of a compound of formula I to a warm-blooded animal in need of such treatment. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 25 to 150 mg of a compound of formula I should be appropriate, whereby, however, the upper limit just given can also be exceeded when this is shown to be indicated.

The following Examples are intended to illustrate the invention, but they are not intended to be limiting in any manner. All temperatures are given in degrees Celsius.

EXAMPLE 1

A mixture of 5.4 g (28.7 mmol) of 2-[3-(methylamino)propyl]benzimidazole, 11.4 g (28.7 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 3.74 g (28.7 mmol) of Hünig base is heated to 120° for 30 minutes. The mixture is thereupon poured into ice-water and extracted with methylene chloride. After drying the organic phase over magnesium sulphate the solvent is evaporated and the residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol as the elution agent. There are thus obtained 6.2 g (49%) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)-propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +41.2°$ (c=0.8%; methanol).

The 2-[3-(methylamino)propyl]benzimidazole used as the starting material was prepared as follows:

22.8 g (91 mmol) of 4-[1-(benzyloxy)-N-methylformamido]butyric acid are dissolved in 200 ml of tetrahydrofuran. The mixture is cooled and 13 ml (128 mmol) of triethylamine and 12 ml (91.5 mmol) of isobutyl chloroformate are added dropwise thereto at −15°. After 2.5 hours 10.3 g (95 mmol) of o-phenylenediamine in 85 ml of tetrahydrofuran are added at −10° within 30 minutes. After stirring at room temperature for 1 hour the solvent is evaporated under reduced pressure. Thereupon, water is added and the mixture is extracted with ethyl acetate. The organic phase is washed with saturated aqeuous sodium bicarbonate solution and saturated aqueous sodium chloride solution. After drying over magnesium sulphate and evaporation of the solvent there are obtained 27.05 g of a product which is chromatographed on silica gel with ethyl acetate as the elution agent. There are thus obtained 20.1 g (71%) of benzyl [3-[(2-aminophenyl)carbamoyl]propyl]methylcarbamate.

MS: M+ 341.

20.1 g (59 mmol) of benzyl [3-[(2-aminophenyl)carbamoyl]propyl]methylcarbamate are dissolved in 450 ml of toluene and treated with 7 g (37 mmol) of p-toluenesulphonic acid. The reaction mixture is thereafter heated to reflux for 2 hours, whereby the water formed is removed from the reaction mixture by means of a water separator. After evaporation and dissolution of the residue in ethyl acetate the solution is washed twice with saturated aqueous sodium bicarbonate solution and twice with saturated aqueous sodium chloride solution. The organic phase is dried over magnesium sulphate and evaporated. Chromatography of the crude product on silica gel with ethyl acetate as the elution agent yields 11 g (58%) of benzyl [3-(2-benzimidazolyl)-propyl]methylcarbamate, m.p. 83°–86°.

11.0 g (34 mmol) of benzyl [3-(2-benzimidazolyl)-propyl]methylcarbamate are reduced with hydrogen in 150 ml of methanol in the presence of 2.5 g of palladium-on-carbon (5%) as the catalyst. There are thus obtained 5.45 g (85%) of 2-[3-(methylamino)propyl]benzimidazole, m.p. 134°–136°.

EXAMPLE 2

6.2 g (14.6 mmol) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol are dissolved in 50 ml of chloroform. 2.5 ml (15 mmol) of N-ethyldiisopropylamine and 5 ml (55 mmol) of methoxyacetyl chloride are added thereto at 0°. The reac-

tion mixture is stirred at room temperature overnight and thereafter treated with 100 ml of 1N sodium hydroxide solution and extracted with chloroform. After drying over magnesium sulphate and evaporation of the solvent the residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol. There are thus obtained 6.2 g of an oil which are dissolved in 30 ml of ethanol and treated with 15 ml of ether saturated with hydrochloric acid. Thereupon, the reaction mixture is evaporated and the residue is crystallized from ethanol/diethyl ether. There are thus obtained 5.4 g (65%) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, m.p. 128°.

EXAMPLE 3

A mixture of 4.2 g (10.35 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 4.5 g (20.7 mmol) of 2-[5-(methylamino)pentyl]benzimidazole is heated to 100° for 30 minutes. Thereafter there are added firstly 100 ml of chloroform, then, after cooling, 100 ml of ether and finally 100 ml of 1N aqueous hydrochloric acid. After stirring for 30 minutes the reaction mixture is made basic with concentrated aqueous sodium hydroxide solution and the organic phase is decanted off, dried and evaporated. After chromatography on silica gel with a 6:1 mixture of methylene chloride and methanol there are obtained 2.7 g (58.2%) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +36.8°$ (c=0.25; methanol).

EXAMPLE 4

6 g (13.2 mmol) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, 20 ml of methoxyacetic anhydride and 1.05 g (13.3 mmol) of pyridine are heated to 0° while stirring. After 2 hours the mixture is cooled and treated with 500 ml of 3N sodium hydroxide solution and 500 ml of methylene chloride and stirred vigorously. The organic phase is dried over magnesium sulphate and evaporated. The residue is dissolved in ethanol and treated with ether saturated with hydrochloric acid. After evaporation and crystallization from ethanol/ether there are obtained 6.2 g (78.5%) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, m.p. 196°-198°.

EXAMPLE 5

The following compounds were prepared in an analogous manner to that described in Examples 1 and 3:

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[4-(methylamino)butyl]benzimidazole the [1S,2S]-2-[2-[[4-(2-benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M+ 437;

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[7-(methylamino)heptyl]benzimidazole the [1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol dihydrochloride, $[\alpha]_{589}^{20} = +32.9°$ (c=1%; methanol);

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[11-(methylamino)undecyl]benzimidazole the [1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 5,6-dimethyl-2-[7-(methylamino)heptyl]benzimidazole the [1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +33.6°$ (c=0.5%; methanol);

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[5-(dodecylamino)pentyl]benzimidazole the [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]-dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M+ 606;

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[7-(methylamino)heptyl]-1H-imidazo[4,5-c]pyridine the [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthalenol, MS: M+ 480.

The benzimidazole derivatives used as the starting materials were prepared in an analogous manner to that described in Example 1.

EXAMPLE 6

The following compounds were prepared by methoxy-acetylating the corresponding hydroxy derivatives in an analogous manner to that described in Examples 2 and 4:

[1S,2S]-2-[2-[[4-(2-Benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_{589}^{20} = +28.6°$ (c=1%; methanol);

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_{589}^{20} = +25.4°$ (c=1%; methanol);

[1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride. $[\alpha]_{589}^{20} = +23.7°$ (c=1%; methanol);

[1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride, (1:1.85), $[\alpha]_{589}^{20} = +26.5°$ (c=1%; methanol);

[1S,2S]-2-[2755 -[[5-(2-benzimidazolyl)pentyl]-dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_{589}^{20} = +22.0°$ (c=0.25%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 112°-115°.

EXAMPLE 7

0.79 g (3.8 mmol) of 2-[3-(methylamino)propyl]benzthiazole, 1.54 g (3.8 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 0.49 g (3.8 mmol) of Hünig base are stirred at 120° for 2.5 hours. After cooling and dissolution of the precipitate with a small amount of methylene chloride the reaction solution is chromato-

graphed on silica gel with a 12:1 mixture of methylene chloride and methanol. There are thus obtained 1.12 g (76%) of [1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M+ 440.

The following compounds were prepared in an analogous manner to that described above:

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 2-[5-(methylamino)pentyl]benzthiazole the [1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2β-naphthalenol, MS: M^+ 468;

starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-28-naphthyl)ethyl p-toluenesulphonate and 2-[7-(methylamino)heptyl]benzthiazole the [1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]ethyl]- 6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M+ 496.

The 2-[3-(methylamino)propyl]benzthiazole used as the starting material was prepared as follows:

5.0 g (19.9 mmol) of 4-[1-(benzyloxy)-N-methylformamido]butyric acid are dissolved in 175 ml of tetrahydrofuran. To the solution, cooled to −20°, are added 2.95 ml (2.1 g; 24 mmol) of triethylamine and 2.95 ml (22 mmol) of isobutyl chloroformate. The reaction mixture is thereafter stirred at this temperature for 1 hour. 2.45 g (19.6 mmol) of 2-aminothiophenol are then added and the reaction mixture is stirred at room temperature for 20 hours. Thereupon, 250 ml of water are added and the mixture is extracted with ethyl acetate. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure. After chromatography on silica gel using a 1:1 mixture of ethyl acetate and hexane there are obtained 1.7 g (25.1%) of benzyl [3-(2-benzthiazolyl)propyl]methylcarbamate as an oil, MS: M+ 340.

1.7 g (4.99 mmol) of benzyl [3-(2-benzthiazolyl)-propyl]methylcarbamate are dissolved at 0° in 40% hydrogen bromide in acetic acid and stirred at room temperature for 20 hours. Thereupon, 60 ml of ether are added and, after 1.5 hours, the precipitate formed is filtered off. After washing the crystalline precipitate with ether and drying there are obtained 1.71 g (93.1%) of 2-[3-(methylamino)propyl]benzthiazole dihydrobromide, m.p. 196°–197°.

The following compounds were prepared in an analogous manner to that described above:

2-[5-(methylamino)pentyl]benzthiazole, MS: M+ 234;

2-[7-(methylamino)heptyl]benzthiazole, MS: M+ 262.

EXAMPLE 8

1.12 g (2.54 mmol) of [1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol are dissolved in 0.2 g of pyridine. 5 ml of methoxyacetic anhydride are added thereto. The reaction mixture is heated to 60° for 2 hours. Thereafter, 100 ml of 1N sodium hydroxide solution are added thereto at 0° and the mixture is extracted with 100 ml of ethyl acetate. The organic phase is dried with magnesium sulphate, filtered and evaporated under reduced pressure. The residue is chromatographed on silica gel using a 30:1 mixture of methylene chloride and methanol. There is thus obtained 0.9 g of an oily product which is dissolved in ethyl acetate and treated with ether saturated with hydrochloric acid. After evaporation to 20 ml, 40 ml of ether are added and the reaction mixture is stirred for 1 hour. The separated precipitate is filtered off and dried. There is thus obtained 0.9 g (64.5%) of [1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, m.p. 130°–134°.

The following compounds were prepared by methoxy-acetylating the corresponding hydroxy derivatives in an analogous manner to that described above:

[1S,2S]-2-[2-[[5-(2-Benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride (5:8), $[\alpha]_{589}^{20} = +27.4°$ (c=0.5%; methanol);

[1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride (4:5), $[\alpha]_{589}^{20} = +25.8°$ (c=1%; methanol).

EXAMPLE 9

In an analogous manner to that described in Examples 1 and 4, starting from (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid via [1S,2S]-2-[2-[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol there was prepared [1S,2S]-2-[2-[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_{589}^{20} = +20.0°$ (c=0.7%; methanol).

The (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid used as the starting material was prepared as follows:

200 g (1.39 mol) of 6-oxoheptanoic acid are dissolved in 1.2 l of methylene chloride. 14 ml of concentrated sulphuric acid are added thereto at −20°. 0.6 l (6.3 mol) of isobutylene is then condensed at −40° and thereupon left to distill into the reaction flask. Thereafter, the reaction mixture is left to react for 6 days at room temperature under the reflux of the reagent. Thereafter. one liter of saturated agueous sodium bicarbonate solution is added thereto while stirring. The aqueous phase is extracted with methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated under reduced pressure. There are thus obtained 268.0 g (1.338 mol; 96.4%) of tert.-butyl 6-oxoheptanoate, which are heated to reflux for 12 hours together with 162.1 g (1.338 mol) of (S)-(−)-1-phenylethylamine and 5.8 g (30.5 mmol) of p-toluenesulphonic acid in 1.9 l of toluene with the simultaneous separation of water. After evaporation of the solvent there are obtained 395.5 g (1.3 mol; 97.4%) of tert.butyl (E/Z)-6-[[(R)-α-methylbenzyl]imino]heptanoate which are dissolved in 7 l of methanol. 43 g of Raney-nickel are added thereto and the mixture is hydrogenated at 10 bar for 24 hours. Thereafter, the mixture is filtered and the solution is evaporated. The resulting 378.5 g of oil are dissolved in 1.1 l of ethylacetate and treated at 0° with 130 ml of 10N ethanolic hydrochloric acid. After stirring at 0° for 1 hour the crystals formed are filtered off and dried. By three-fold recrystallization of the resulting 282 g of crystals from ethyl acetate there are obtained 172.7 g (38.9%) of tert.butyl (S)-6-[[(S)-α-methylbenzyl]amino]hexanoate hydrochloride, m.p. 154°–156°.

160 g (0.648 mol) of the above hydrochloride are dissolved in 2.4 l of ethanol and hydrogenated at 10 bar in the presence of 20 g of palladium-on-carbon (5%). After filtering off the catalyst the solvent is evaporated and the residue is crystallized from 560 ml of ethyl acetate and 240 ml of hexane. There are thus obtained

101 g (90.8%) of tert.-butyl (S)-6-aminoheptanoate hydrochloride, m.p. 107°–109°.

89 g (374 mmol) of tert.butyl (S)-6-aminoheptanoate hydrochloride are dissolved in 1.3 l of methylene chloride. The solution is saturated with hydrogen chloride and heated to reflux for 4 hours. After filtering off and drying the precipitate formed there are obtained 60.8 g (89.5%) of (S)-6-aminoheptanoic acid hydrochloride, m.p. 157°–160°.

To 30 g (166 mmol) of (S)-6-aminoheptanoic acid hydrochloride in 57 ml of water are added 57 ml of 4N aqueous sodium hydroxide solution and thereafter dropwise simultaneously at 10° 92 ml of 4N aqueous sodium hydroxide solution and 42 ml (294 mol) of benzyl chloroformate so that the pH value always lies between 10 and 12. After the precipitation of the product the mixture is stirred at 0° for a further 2 hours. Thereafter, 300 ml of water are added and the reaction mixture is extracted with ether. The aqueous phase is then acidified with 20 ml of concentrated hydrochloric acid and extracted with methylene chloride. The methylene chloride phase is dried over magnesium sulphate and evaporated. The crystals obtained are recrystallized from chloroform/hexane, whereby there are obtained 33.1 g (72%) of (S)-6-[1-(benzyloxy)formamido]heptanoic acid, m.p. 82°–83°.

6.5 g (23 mmol) of (S)-6-[1-(benzyloxy)formamido]-heptanoic acid are added to a suspension of 3.05 g of 55% sodium hydride (70 mmol) in 200 ml of dimethylformamide and the mixture is left to react at 40° for 30 minutes. Thereafter, 13 g (90 mmol) of methyl iodide are added dropwise and the reaction mixture is heated to 70° for 1 hour. After evaporation of the solvent 120 ml of 1N agueous sodium hydroxide solution and 120 ml of ethanol are added and the reaction mixture is heated to reflux for 30 minutes. Thereafter, the mixture is evaporated to half, 100 ml of saturated aqueous sodium bicarbonate solution are added and the mixture is extracted with ethyl acetate. The aqueous phase is acidified and extracted with methylene chloride. The organic phase is dried over magnesium sulphate and evaporated. The residue (5 g) is chromatographed on silica gel with a 12:1 mixture of methylene chloride and methanol, whereby there are obtained 3.5 g (52.2%) of (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid, MS: M+ 293.

EXAMPLE 10

A mixture of 1.4 g (3.33 mmol) of 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthyl-]ethyl p-toluenesulphonate and 1.63 g (6.66 mmol) of 2-[7-(methylamino)heptyl]benzimidazole is heated to 100° for 30 minutes. The mixture is thereafter poured into 100 ml of water and extracted with 100 ml of ethyl acetate. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure, and the residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol. There is thus obtained a yellowish oil (1 g) which is dissolved in 20 ml of ethanol and treated with 2 ml of ether saturated with hydrochloric acid. The mixture is then evaporated under reduced pressure and the residue is crystallized from ethyl acetate/ethanol/ether and dried, whereby there is obtained 0.7 g (37.2% of [1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxynaphthalenol dihydrochloride, m.p. 179°–181°.

The 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methyoxy-2-naphthyl]ethyl p-toluenesulphonate used as the starting material was prepared as follows:

A mixture of 5.04 g (20 mmol) of 6997 -fluoro-1,2,3,4-tetrahydro-2-isopropyl-2-hydroxy-1α-isopropyl-2β-naphthylethanol, 6.13 g (22 mmol) of triphenylchloromethane and 50 ml of pyridine is stirred at room temperature for 20 hours. The reaction mixture is thereafter poured into 500 ml of ice-water and extracted with 400 ml of ether. The ether extracts are washed with 400 ml of 1N aqueous hydrochloric acid, 400 ml of saturated aqueous sodium bicarbonate solution and 400 ml of water. After drying over magnesium sulphate the ether is evaporated under reduced pressure. There are obtained 8.25 g (83%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-(trityloxy)ethyl]-2-naphthalenol. 8 g (16.2 mmol) of this compound are dissolved in 300 ml of tetrahydrofuran and treated at −20° with 35.6 mmol of freshly prepared lithium diisopropylamide. Thereafter, 9.2 g (64.8 mmol) of methyl iodide are added and the reaction mixture is stirred at room temperature for 20 hours. The reaction mixture is poured into ice-water and extracted with methylene chloride. The organic phase is dried over magnesium sulphate and the solvent is evaporated under reduced pressure. After chromatography on silica gel using a 1:2 mixture of methylene chloride and hexane and recrystallization from hexane there are obtained 4.15 g (54.7%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-[2-trityloxy)ethyl]naphthalenol, m.p. 132°–134°.

4.15 g (8.16 mmol) of the above compound are left to stand at 0° for 2 hours with 15 ml of ether saturated with hydrochloric acid. After evaporation of the solvent and chromatography of the residue on silica gel using a 1:2 mixture of ethyl acetate and hexane there is obtained 1.0 g (47%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthylethanol, $[\alpha]_{589}^{20} = +65.6°$ (c=0.25%; methanol).

0.98 g (3.7 mmol) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthylethanol is dissolved in 6 ml of pyridine and left to react at 0° for 1 hour with 1.06 g (5.6 mmol) of toluene-4-sulphochloride. The reaction mixture is thereafter poured into 100 ml of water and extracted with 200 ml of ether. The ether extract is washed with 100 ml of 1N aqueous hydrochloric acid, 100 ml of saturated aqueous sodium bicarbonate solution and 100 ml of water. After drying the ethereal solution over magnesium sulphate and evaporation of the solvent there are obtained 1.50 g (97.4%) of 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthyl]ethyl p-toluenephonate, $[\alpha]_{589}^{20} = +42.6$ (c=0.5%; methanol).

EXAMPLE 11

2.0 g (4.43 mmol) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)phenyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol dissolved in 30 ml of tetrahydrofuran are added to a suspension of 436 mg (10 mmol) of 55% sodium hydride in 20 ml of tetrahydrofuran. After stirring at room temperature for 45 minutes 1.42 g (10 mmol) of methyl iodide are added thereto. After a further hour, water and methylene chloride are added and the reaction mixture is shaken vigorously. The organic phase is dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol, whereby there are obtained 1.2 g (60%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopro-

pyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthalenol, MS: M+ 465.

[1S,2S]-2-[2-[[7-(1-Dodecyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol was prepared in analogous manner to that described above by reaction with dodecyl iodide.

EXAMPLE 12

A mixture of 1.2 g (2.58 mmol) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthalenol, 206 mg (2.6 mmol) of pyridine and 4 ml of methoxyacetic anhydride is heated to 70° for 2 hours. Thereafter, 100 ml of 3N aqueous sodium hydroxide solution are added thereto and the mixture is extracted with 100 ml of methylene chloride. The organic phase is dried over magnesium sulphate and evaporated. The product is chromatographed on silica gel using a 15:1 mixture of methylene chloride and methanol. The resulting 550 mg of oil are dissolved in 50 ml of ethyl acetate and treated with 1 ml of ether saturated with hydrochloric acid. After evaporation of the solvent the residue is crystallized from ethyl acetate/ether, whereby there are obtained 600 mg (41%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 203°–205°.

[1S,2S]-2-[2-[[7-(1-Dodecyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_{589}^{20} = +20.4°$ (c=0.9%; methanol), was prepared in an anaoogous manner to that described above.

EXAMPLE 13

0.425 g (1 mmol) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate is dissolved in 60 ml of methanol and subsequently treated with 10 ml of 6% hydrogen peroxide and 50 mg (0.15 mmol) of sodium tungstate. After stirring at room temperature for 20 hours 100 mg of platinum-on-carbon (5%) in 2 ml of water are added thereto and the mixture is stirred for a further hour. Thereupon, the mixture is filtered, the filtrate is concentrated, the residue is diluted with a small amount of methylene chloride and the mixture is chromatographed on silica gel with a 15:1 mixture of methylene chloride and methanol as the elution agent. There are thus obtained 0.18 g (35.2%) of a first diastereomer of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methyl-N -oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate with a R_f value of 0.33, $[\alpha]_{589}^{20} = +39.4°$ (c=0.5%; methanol), and 0.276 g (54%) of a second diasteromer of the named compound with a R_f value of 0.26 (methylene chloride/methanol 6:1), $[\alpha]_{589}^{20} = +34.8°$ (c=0.5%; methanol).

EXAMPLE 14

5.0 g (12.3 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 4.0 g (24.6 mmol) of 2-methylaminobenzthiazole are heated to 120° for 30 minutes. Thereafter, 50 ml of a 12:1 mixture of methylene chloride and methanol are added and the reaction mixture is purified by column chromatography on silica gel using a 1:1 mixture of hexane and ethyl acetate as the elution agent. In this manner there are obtained 3.22 g (65.7%) of [1S,2S]-2-[2-[(2-benzthiazolyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, m.p. 102°–103°.

EXAMPLE 15

6.1 g (15 mmol) of [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 6.8 g (30 mmol) of 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride are stirred at 130° for 4.5 hours in a mixture of 30 ml of dimethylformamide and 30 ml of N-ethyldiisopropylamine. The reaction mixture is poured into 600 ml of ice-water and extracted with 700 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained product is chromatographed on 150 g of silica gel with methylene chloride and 0–10% isopropanol as the elution agent, whereby 5.2 g (72%) of 1-[2-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]ethyl]-2-benzimidazolinone are obtained as an oil.

The 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride used as the starting material was prepared as follows:

93.8 ml (150 mmol) of a n-butyllithium solution (about 1.6M in hexane) are added dropwise at 0°–5° to 24.8 g (150 mmol) of 2-(N-benzyl-N-methylamino)ethanol dissolved in 250 ml of absolute tetrahydrofuran. After stirring at 0° for 15 minutes 11.7 ml (150 mmol) of methanesulphochloride in 50 ml of tetrahydrofuran are added dropwise at a temperature between 0° and 5° and the reaction mixture is stirred at 0° for 30 minutes.

5.8 g (133 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and suspended in 40 ml of dimethylformamide. 23.1 g (132.5 mmol) of 1-(1-methylvinyl)benzimidazolin-2-one in 90 ml of dimethylformamide are subsequently added dropwise at room temperature and the reaction mixture is stirred for a further 15 minutes.

This reaction mixture is added dropwise at 0° to the reaction solution described above. Thereafter, the mixture is heated to 70° and stirred for 3 hours. The reaction mixture is subsequently poured into 1 l of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained product is chromatographed on 500 g of silica gel with methylene chloride and 0–5% isopropanol as the elution agent, whereby there are obtained 26.8 g (63%) of 1-(1-methylvinyl)-3-[2-(N-benzyl-N-methylamino)ethyl]-2-benzimidazolinone as an oil.

26.5 g (82.5 mmol) of the above-named compound are dissolved in 265 ml of ethanol, treated with 26.5 ml of concentrated aqueous hydrochloric acid while stirring and heated to reflux for 1 hour. After cooling the reaction mixture to 5°, 1-[2-(N-benzyl-N-methylamino)ethyl]-2-benzimidazolinone crystallizes out in the form of the hydrochloride, m.p. 107°–109°; yield 24.2 g (92%).

22.9 g (72 mmol) of 1-[2-(N-benzyl-N-methylamino)ethyl]-2-benzimidazolinone hydrochloride are dissolved in 250 ml of methanol, treated with 2.5 g of palladium-on-carbon (10%) and hydrogenated at room temperature for 90 minutes. The residue obtained after filtration and concentration is recrystallized from methanol/ether, whereby there are obtained 15.5 g (94%) of 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride, m.p. 177°–180°.

EXAMPLE 16

4.57 g (10.7 mmol) of 1-[2-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]ethyl]-2-benzimidazolinone are dissolved in 15 ml of methylene chloride, treated with 2.2 ml of pyridine and 7.0 g (43 mmol) of methoxyacetic anhydride and stirred at room temperature for 20 hours. Thereafter, the mixture is treated with 30 ml of 3N sodium hydroxide solution while cooling with ice and stirred at room temperature for 15 minutes. The reaction mixture is subsequently poured into 400 ml of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and concentrated. There are thus obtained 6.9 g of an oil (N,O-diacylated product) which are dissolved in 30 ml of methanol and treated at room temperature with 11.5 ml of 1N aqueous sodium hydroxide solution. After stirring for 30 minutes the mixture is poured into 400 ml of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water. dried over potassium carbonate, evaporated, treated with one equivalent of hydrochloric acid in methanol, again evaporated and finally recrystallized from methanol/ether. There are thus obtained 3.9 g (72%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[2-(2-oxo-1-benzimidazolinyl)ethyl-]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, m.p. 130°–133° (dec.); $[\alpha]_D^{20} = +26.0°$ (c=1%; methanol).

EXAMPLE 17

In analogy to Example 15, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate with 1-[6-(methylamino)hexyl]-2-benzimidazolinone there was obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl- 2-naphthyl]ethyl]methylamino]-hexyl]-2-benzimidazolinone as an oil.

The 1-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

17.6 g (150 mmol) of 6-amino-1-hexanol dissolved in 50 ml of methanol are added dropwise at room temperature to 32.7 g (150 mmol) of di-tert.-butyl dicarbonate in 100 ml of methanol. After stirring at room temperature for 4 hours the reaction mixture is evaporated, whereby there are obtained 36.6 g of tert.-butyl (6-hydroxyhexyl)carbamate as an oil which is used directly in the next step.

34.8 g of tert.-butyl (6-hydroxyhexyl)carbamate are dissolved in 250 ml of methylene chloride and treated at 0° with 24.0 ml (174 mmol) of triethylamine. Subsequently, 12.9 ml (166 mmol) of methanesulphochloride in 50 ml of methylene chloride are added dropwise at −60° within 15 minutes and the reaction mixture is subsequently stirred at −60° for 90 minutes. Thereafter, the reaction solution is poured into 600 ml of ice-water and extracted with 800 ml of methylene chloride. The organic extract is washed with water, dried over magnesium sulphate and evaporated. There are thus obtained 58.6 g of tert.-butyl [6-[(methylsulphonyl)oxy]-hexyl]carbamate as an oil which is processed without purification.

5.9 g (135 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and subsequently covered with 100 ml of dimethylformamide. To this suspension are added dropwise at room temperature 22.3 g (128 mmol) of 1-(1-methylvinyl)benzimidazolin-2-one in 100 ml of dimethylformamide. After stirring at room temperature for 2 hours 55.0 g of tert.-butyl [6-[(methylsulphonyl)oxy]hexyl]carbamate in 100 ml of dimethylformamide are added dropwise and the reaction mixture is stirred at room temperature for 18 hours. Thereafter. the reaction mixture is poured into 1 l of water and extracted with 750 ml of methylene chloride. The organic extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained residue is chromatographed on 950 g of silica gel with methylene chloride/hexane, methylene chloride and a 95:5 mixture of methylene chloride and isopropanol as the elution agent, whereby there are obtained 45.3 g of tert.-butyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimidazolinyl]hexyl]carbamate as an oil.

5.3 g (121 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and subsequently covered with 100 ml of dimethylformamide. To this suspension are added dropwise at room temperature 45.0 g (121 mmol) of tert.-butyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimiaazolinyl]hexyl]carbamate and the reaction mixture is stirred at this temperature for 90 minutes. Subsequently, 9.0 ml (155 mmol) of methyl iodide in 50 ml of dimethylformamide are added dropwise at 10° and the reaction mixture is stirred at 10° for 1 hour and at room temperature for 16 hours. Thereafter, the reaction solution is poured into 800 ml of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained residue is chromatographed on 500 g of silica gel with hexane/ethyl acetate (4:1 and 1:1), whereby there are obtained 39.1 g of tert.-butyl methyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimidazolinyl]hexyl]carbamate as an oil.

38.8 g (100 mmol) of the last-named compound are dissolved in 300 ml of absolute ethanol, treated while stirring with 40 ml of concentrated aqueous hydrochloric acid and heated to reflux for 75 minutes. After cooling to 40° the reaction mixture is concentrated under reduced pressure and poured into 500 ml of ice-water. The aqueous phase is adjusted to pH 8–9 by the addition of concentrated aqueous ammonia solution and extracted with 600 ml of methylene chloride. The extract is washed with water and subsequently discarded. The combined aqueous phases are adjusted to pH 10–11 with 3N aqueous sodium hydroxide solution and extracted six times with 150 ml of methylene chloride/isopropanol (4:1) each time. The combined extracts are dried over potassium carbonate and evaporated, whereby there are obtained 21.6 g of 1-[6-(methylamino)hexyl]-2-benzimidazolinone as an oil.

EXAMPLE 18

In analogy to Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone there is obtained 1-[6-[[2-[[7S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]-hexyl]-3-methyl-2-benzimidazolinone as an oil.

The 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

A solution of 9.7 g (44.5 mmol) of di-tert.-butyl dicarbonate in 50 ml of methanol is added dropwise at room temperature to 10.0 g (40.4 mmol) of 1-[6-(methylamino)hexyl]-2-benzimidazolinone in 150 ml of methanol and the reaction mixture is stirred at room

temperature for 16 hours. Thereafter, 6.9 ml (49.5 mmol) of triethylamine and a further 9.7 g of di-tert.-butyl dicarbonate in 50 ml of methanol are added and the mixture is stirred at room temperature for a further 16 hours. Thereafter, the reaction mixture is poured into 200 ml of water and extracted with 400 ml of methylene chloride. The extracts are washed with water, dried over potassium carbonate and evaporated, whereby there are obtained 14.1 g of tert.-butyl methyl [6-(2-oxo-1-benzimidazolinyl)hexyl]carbamate as an oil.

2.6 g (59.6 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and subsequently covered with 30 ml of dimethylformamide. To this suspension are added dropwise at room temperature within 20 minutes 13.8 g (39.7 mmol) of tert.-butyl methyl [6-(2-oxo-1-benzimidazolinyl)hexyl]carbamate in 90 ml of dimethylformamide. After stirring at room temperature for 90 minutes, 6.2 ml (99.3 mmol) of methyl iodide in 30 ml of dimethylformamide are added dropwise at room temperature and the reaction mixture is stirred at this temperature for a further 16 hours. For the work-up, the mixture is poured into 200 ml of water and extracted with 300 ml of methylene chloride. The methylene chloride extract is washed with water, dried over potassium carbonate and concentrated. The residue is chromatographed on 110 g of silica gel with methylene chloride and methylene chloride/isopropanol (99:1 and 98:2), whereby there are obtained 9.0 g of tert.-butyl methyl [6-(3-methyl-2-oxo-1-benzimidazolinyl)hexyl]carbamate as an oil.

In analogy to Example 17, last paragraph, from the compound obtained above there was obtained 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone as an oil.

EXAMPLE 19

In an analoqous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[p-[4-(methylamino)butyl]phenyl-]imidazole there was obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl- 2-[2-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthalenol as an oil.

The 1-[p-[4-(methylamino)butyl]phenyl]imidazole used as the starting material was prepared as follows:

(a) 53.1 g (116 mmol) of [2-(m-dioxan-2-yl)ethyl]triphenylphosphonium bromide are suspended in 160 ml of tetrahydrofuran and treated at −25° within 15 minutes with 77.3 ml (116 mmol) of n-butyllithium solution (about 1.5M in hexane). Thereafter, the mixture is stirred at −25° for 15 minutes. Subsequently, 10 ml of a mixture of tetrahydrofuran and 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (1:1) are added, the mixture is stirred at −25° for a further 5 minutes and then treated within 30 minutes at −25° with 20 g (116 mmol) of p-(imidazol-1-yl)-benzaldehyde in 150 ml of tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (1:1). After completion of the addition the reaction mixture is warmed to room temperature and stirred at this temperature for 15 minutes. Thereafter, the reaction mixture is poured into 1 l of ice-water and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water, dried over magnesium sulphate and evaporated. There are thus obtained 42.2 g of a semi-crystalline product which is dissolved in 600 ml of methanol and hydrogenated exhaustively in the presence of 18 g of palladium-on-carbon (5%). After filtering off the catalyst and evaporation of the filtrate there are obtained 36.6 g of a semi-crystalline residue which, in turn, is dissolved in 700 ml of methanol, treated with 22.4 g of p-toluenesulphonic acid monohydrate and heated to reflux for 2.5 hours. After cooling to room temperature the pH value is adjusted to 7 with 36 g of sodium carbonate, the reaction mixture is evaporated, the residue is poured into 500 ml of water and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water and saturated sodium chloride solution, dried over magnesium sulphate and evaporated, whereby there are obtained 36.1 g of a semi-crystalline residue. This is dissolved in 400 ml of tetrahydrofuran, treated with 110 ml of 3N aqueous hydrochloric acid, stirred at room temperature for 3 hours and subsequently concentrated under reduced pressure. Thereafter, the reaction mixture is poured into 500 ml of ice-water and extracted three times with 200 ml of ether each time. The aqueous phase is subsequently adjusted to pH 9 with potassium carbonate and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water, dried over potassium carbonate and evaporated. The residue is chromatographed on 240 g of silica gel with methylene chloride and 0-5% isopropanol as the elution agent. There are thus obtained 13.2 g (53%) of 4-[p-(imidazol-1-yl)phenyl]butanal as an oil.

(b) 37.8 g (558 mmol) of methylamine hydrochloride are dissolved in 200 ml of methanol and thereupon treated with 45.8 g (558 mmol) of sodium acetate and 3.9 g (62.1 mmol) of sodium cyanoborohydride. The reaction mixture is stirred at room temperature for 15 minutes and thereafter 12.05 g (56.24 mmol) of 4-[p-(imidazol-1-yl)phenyl]butanal in 40 ml of methanol are added dropwise at room temperature within 15 minutes and the reaction mixture is stirred at room temperature for 3 hours. Thereafter, the reaction mixture is concentrated under reduced pressure, the residue is poured into 1 l of ice-water and extracted with 800 ml of methylene chloride. The organic extract is washed with water, dried over magnesium sulphate and evaporated. The residue obtained is chromatographed on 100 g of silica gel with methylene chloride/isopropanol/aqueous, 25% ammonia (160:40:1 and 7:3:0.3, respectively), whereby there are obtained 3.8 g (29%) of 1-[p-[4-(methylamino)butyl]phenyl]imidazole as an oil.

EXAMPLE 20

In an analogous manner to that described in Example 15, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[4-(methylamino)butyl]-2-benzimidazolinone there was obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone as an oil.

The 1-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared as follows:

In analogy to Example 17, from 4-(methylamino)-1-butanol there was obtained tert.-butyl methyl [4-[(methylsulphonyl)oxy]butyl]carbamate as an oil which was then converted into tert.-butyl methyl [4-[3-(1-methylvinyl)-2-oxo-1-benzimidazolinyl]butyl]carbamate. This compound, likewise obtained as an oil, was then converted, again in analogy to Example 17, into 1-[4-(methylamino)butyl]-2-benzimidazolinone which was again obtained as an oil.

EXAMPLE 21

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone there was obtiined 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-isopropyl-2-benzimidazolinone as an oil.

The 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared as follows:

8.14 g (22.6 mmol) of tert.-butyl methyl [4-[3-(1-methylvinyl)-2-oxo-1-benzimidazolinyl]butyl]carbamate are dissolved in 80 ml of methanol and, after the addition of 1.6 g of palladium-on-carbon (5%), hydrogenated for 4 hours. Thereupon, the reaction mixture is filtered and evaporated, whereby there are obtained 8.5 g of tert.-butyl methyl [4-(3-isopropyl-2-oxo-1-benzimidazolinyl)butyl]carbamate as an oil. This is converted in analogy to the last paragraph of Example 17 into 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone which is likewise obtained as an oil.

EXAMPLE 22

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone there was obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-butyl-2-benzimidazolinone as an oil.

The 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

In analogy to Example 18, from tert.-butyl methyl [6-(2-oxo-1-benzimidazolinyl)hexyl]carbamate and butyl iodide there was obtained tert.-butyl methyl [6-(3-butyl-2-oxo-1-benzimidazolinyl)hexyl]carbamate as an oil. This compound was converted in analogy to Example 17 into 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone which was likewise obtained as an oil.

EXAMPLE 23

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-(2-morpholinoethyl)-3-[6-(methylamino)hexyl]-2-benzimidazolinone there was obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]-hexyl]-3-(2-morpholinoethyl)-2-benzimidazolinone as an oil.

The 1-(2-morpholinoethyl)-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

9.0 g (25.9 mmol) of tert.-butyl methyl [6-(2-oxo-1-benzimidazolinyl)hexyl]carbamate are dissolved in 250 ml of methanol and treated with 35 g (259 mmol) of potassium carbamate, 0.5 g of potassium iodide and portionwise with 16.9 g (90.6 mmol) of chloroethylmorpholine hydrochloride. Thereafter, the reaction mixture is heated to reflux for 16 hours. After cooling the reaction mixture is poured into 1 l of ice-water and extracted with 800 ml of methylene chloride. The extract is washed with water, dried and concentrated. The residue is dissolved in 50 ml of ether and extracted in each case once with 15 ml and 5 ml of 3N methanesulphonic acid in water and once with 5 ml of water. The combined aqueous phases are adjusted to pH 8–9 With ammonia and extracted three times with 100 ml of methylene chloride each time. The combined extracts are washed with water, dried over potassium carbonate and evaporated, whereby there are obtained 7.8 g (65.4%) of tert.-butyl methyl [6-[3-(2-morpholinoethyl)-2-oxo-1-benzimidazolinyl]hexyl]carbamate as an oil.

This was then converted, likewise in analogy to Example 17, into 1-(2-morpholinoethyl)-3-[6-(methylamino)hexyl]-2-benzimidazolinone dihydrochloride, m.p. 229°–232°.

EXAMPLE 24

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-benzyl-3-[4-(methylamino)butyl]-2-benzimidazolinone there was obtained 1-benzyl-3-[4-[[2-[[1S,2S]-6-fluoro-1.2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone as an oil.

The 1-benzyl-3-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared in analogy to Example 18 from 1-[4-(methylamino)butyl]-2-benzimidazolinone via tert.-butyl methyl [4-(2-oxo-1-benzimidazolinyl)butyl]carbamate.

EXAMPLE 25

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[4-(methylamino)butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone there was obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone as an oil.

The 1-[4-(methylamino)butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone used as the starting material was prepared in analogy to Example 18 from tert.-butyl methyl [4-(2-oxo-1-benzimidazolinyl)butyl]carbamate.

EXAMPLE 26

In an analogous manner to that described in Example 15, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1,3-dihydro-3-[6-(methylamino)hexyl]-2H-imidazo[4,5-c]pyridin-2-one there was obtained 3-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-1,3-dihydro-2H-imidazo[4.5-c]pyridin-2-one as an oil.

The 1,3-dihydro-3-[6-(methylamino)hexyl]-2H-imidazo[4.5-c]pyridin-2-one used as the starting material was prepared as follows:

In an analogous manner to that described in Example 17, from 6-(methylamino)-1-hexanol there was obtained tert.-butyl methyl (6-hydroxyhexyl)carbamate as an oil which was then converted via tert.-butyl methyl [6-[(methylsulphonyl)oxy]hexyl]carbamate, likewise obtained as an oil, into tert.-butyl methyl [6-[1-(1-methylvinyl)-1,2-dihydro-2-oxo-3H-imidazo[4,5-c]pyridin-3-yl]hexyl]carbamate; the product was again obtained as an oil.

12.2 g (31.4 mmol) of the last-named compound are dissolved in 100 ml of ethanol, treated with 13 ml of concentrated aqueous hydrochloric acid and heated to

reflux for 40 hours. Thereafter, the mixture is adjusted to pH 9–10 with dilute aqueous sodium hydroxide solution while cooling with ice, the reaction solution is saturated with sodium chloride and extracted continuously with chloroform for 16 hours. The extract is dried over potassium carbonate and evaporated, whereby there are obtained 7.2 g (92%) of 1,3-dihydro-3-[6-(methylamino)hexyl]-2H-imidazo[4,5-c]pyridin-2-one as an oil which is processed without further purification.

EXAMPLE 27

The following compounds were prepared in an analogous manner to that described in Example 16:

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(2-oxo-1-benzimidazolinyl)hexyl]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +27.8°$ (c=1%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(2-oxo-1-benzimidazolinyl)butyl]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +28.7°$ (c=1%; methanol);

[1S,2S]-2-[2-[[6-(1,2-dihydro-2-oxo-3H-imidazo[4,5-c]pyridin-3-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_D^{20} = +26.0°$ (c=1%; methanol).

EXAMPLE 28

4.6 g (9.3 mmol) of 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]-methylamino]hexyl]-3-methyl-2-benzimidazolinone are dissolved in 15 ml of methylene chloride, treated with 1.9 ml of pyridine and 6.2 g (38 mmol) of methoxyacetic anhydride and stirred at room temperature for 20 hours. Thereafter, the mixture is treated with 45 ml of 1N aqueous sodium hydroxide solution while cooling with ice and stirred at 10°–15° for 1 hour. The reaction mixture is subsequently poured into 400 ml of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate, evaporated, treated with one equivalent of hydrochloric acid in ethanol and evaporated. There are thus obtained 5.3 g of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-methyl-2-oxo-1-benzimidazolinyl)hexyl]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +27.1°$ (c=1%; methanol).

EXAMPLE 29

The following compounds were manufactured in analogy to Example 28:

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthyl methoxyacetate oxalate (1:1), $[\alpha]_D^{20} = +27.6°$ (c=1%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(3-isopropyl-2-oxo-1-benzimidazolinyl)-butyl]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +27.6°$ (c=1%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-butyl-2-oxo-1-benzimidazolinyl)hexyl-]amino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +26.4°$ (c=1%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-[3-(2-morpholinoethyl)-2-oxo-1-benzimidazolinyl]hexyl]amino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_D^{20} = +22.4°$ (c=1%; methanol);

[1S,2S]-2-[2-[[4-(3-benzyl-2-oxo-1-benzimidazolinyl)-butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_D^{20} = +25.6°$ (c=1%; methanol);

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-[2-oxo-3-(2-pyridylmethyl)-1-benzimidazolinyl]butyl]amino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, $[\alpha]_D^{20} = +23.3°$ (c=1%; methanol).

EXAMPLE 30

1.3 g (3.1 mmol) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol in 10 ml of dimethylformamide are treated at room temperature with 0.19 g (1,53 mmol) of 4-dimethylaminopyridine, 1.7 ml (12.3 mmol) of triethylamine and a solution of 0.96 ml (9.24 mmol) of isobutyryl chloride in 5 ml of dimethylformamide and stirred at room temperature for 2 hours. Thereafter, the reaction mixture is poured into 20 ml of ice-water, treated with 10 ml of 1N aqueous sodium hydroxide solution, stirred at 0° for 10 minutes and extracted with 100 ml of methylene chloride. The extract is washed with water. dried over potassium carbonate and evaporated. The thus-obtained product is dissolved in 20 ml of methanol, treated with 1.5 ml of 1N aqueous sodium hydroxide solution, stirred at room temperature for 1 hour, poured into 50 ml of water and extracted with 100 ml of methylene chloride. The extract is washed with water, dried over magnesium sulphate and evaporated. The residue is chromatographed on 30 g of silica gel with methylene chloride and 1–20% isopropanol and on 20 g of silica gel with methylene chloride/isopropanol/25% aqueous ammonia (9:1:0.1). There are thus obtained 360 mg (21%) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl isobutyrate dihydrochloride.

EXAMPLE 31

A solution of 2.32 g (0.005 mol) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthalenol and 0.6 g (0 005 mol) of phenyl isocyanate in 5 ml of toluene is treated with 7.5 mg of tin(II) 2-ethylhexanoate and heated to 100° for 15 hours. After concentration under reduced pressure the oily residue is chromatographed on 160 g of silica gel with methanol/-methylene chloride (3:2) as the elution agent. The oily product obtained is dissolved in methylene chloride and treated with an excess of hydrogen chloride in ether. There are obtained 2.15 g (65%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl carbanilate dihydrochloride, m.p. 157°–160°, as a colourless crystalline powder.

EXAMPLE 32

The following compounds were obtained in an analogous manner to that described in Example 31:

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl butylcarbamate dihydrochloride, m.p. 156°–158°;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl benzylcarbamate dihydrochloride, m.p. 132°–136°;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl[5-(1-methyl-2-benzimidazolyl)pentyl-]amino]ethyl]-2-naphthyl p-chlorocarbanilate dihydrochloride, m.p. 159°–163°.

EXAMPLE 33

A mixture of 4.67 g (11.5 mmol) of [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate, 3.5 g (11.5 mmol) of 1-methyl-2-[3-(methylamino)propyl]-4,5-diphenylimidazole and 1.5 g (11.5 mmol) of N-ethyl-diisopropylamine is stirred at 100° for 1 hour. The cooled mass is partitioned between water and methylene chloride and the organic phase is washed with a saturated solution of sodium chloride. dried over sodium sulphate and concentrated to dryness. The residual oil is chromatographed on 400 g of silica gel with methylene chloride/methanol (4:1) as the elution agent. The purified condensation product (5.3 of oil) is dissolved in 15 ml of methoxyacetic anhydride, treated with 0.85 ml of pyridine and the solution is stirred at 70° for 2 hours. The cooled reaction mixture is partitioned between 400 ml of methylene chloride and 400 ml of 3N aqueous sodium hydroxide solution and the mixture is stirred intensively at room temperature for 15 minutes. The separated aqueous phase is again extracted with 400 ml of methylene chloride, the combined extracts are washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness. The oily residue is chromatographed on 350 g of silica gel with methylene chloride/methanol (9:1) as the elution agent. The oil obtained from the homogeneous fractions is dissolved in ethyl acetate and treated with an excess of hydrogen chloride in ether. The crystallizate is filtered off, washed with ether and dried. There are obtained 4.0 g (51%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 185°–189°, as an almost colourless crystalline powder.

The 1-methyl-2-[3-(methylamino)propyl]-4,5-diphenylimidazole used as the starting material was prepared as follows:

3.2 ml (0.024 mol) of isobutyl chloroformate are added dropwise at −5° to a solution of 7.0 g (0.024 mol) of 4,5-diphenylimidazole-2-propionic acid and 3.36 ml (0.024 mol) of triethylamine in 80 ml of dimethylformamide. After stirring at 0°–5° for 30 minutes 1.64 g (0.024 mol) of methylamine hydrochloride and 3.36 ml (0.024 mol) of triethylamine in 32 ml of dimethylformamide and 1.65 ml of water are added. The temperature is then left to rise to room temperature and the mixture is stirred for a further 20 hours. After concentration under reduced pressure the residue is boiled up in 250 ml of methanol and treated with 3.6 ml (0.024 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), whereby a clear solution results. 4.8 g of N-methyl-4.5-diphenylimidazole-2-propionamide, m.p. 195°–200° (dec.), result by cooling in an ice-bath. From the mother liquor there are obtained by concentration and treatment with water a further 2 g of the same product, m.p. 195°–200°. Total yield: 6.8 g (93%).

9.15 g (0.03 mol) of N-methyl-4,5-diphenylimidazole-2-propionamide are added portionwise to a stirred suspension of 2.3 g (0.06 mol) of lithium aluminium hydride in 160 ml of tetrahydrofuran and the mixture is subsequently heated to reflux for 4 hours. At 5°–10° there are added dropwise thereto 6 ml of water, then 9 ml of a 10% solution of potassium hydroxide and again 6 ml of water. The precipitate is filtered off and boiled up three times with 50 ml of tetrahydrofuran each time. The combined filtrates are washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness under reduced pressure. The oily residue is chromatographed on 200 g of silica gel firstly with chloroform/ethanol (9:1) and then with methanol as the elution agent. The first fractions which are eluted homogeneous give, after evaporation and tritutation with ether, 1.2 g of starting material. The following fractions which are eluted homogeneous yield, after the same treatment, 5.5 g (73%) of 2-[3-(methylamino)propyl]-4,5-diphenylimidazole in the form of colourless crystals, m.p. 110°–113°.

A solution of 5.25 g (0.018 mol) of 2-[3-(methylamino)propyl]-4,5-diphenylimidazole and 3.8 ml (0.028 mol) of benzyl chloroformate in 38 ml of dimethylformamide is treated with 5 g of finely ground dry potassium carbonate and thereupon stirred intensively at room temperature for 1 hour. The inorganic salts are then filtered off, washed with methylene chloride and the filtrate is concentrated to dryness under reduced pressure. The oily residue is chromatographed on 500 g of silica gel with ethyl acetate as the elution agent. The homogeneous fractions give, after evaporation and trituration of the residue with hexane, 6.5 g (85%) of 2-[3-(N-benzyloxycarbonylmethylamino)propyl]-4,5-diphenylimidazole in the form of colourless crystals, m.p. 105°–108°.

A solution of 6.4 g (0.015 mol) of 2-[3-(N-benzyloxycarbonylmethylamino)propyl]-4,5-diphenylimidazole in 120 ml of dimethylformamide is treated at 15°–20° under argon with 0.018 mol of sodium hydride (0.8 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 1.85 ml (0.03 mol) of methyl iodide in 10 ml of dimethylformamide is added thereto at 15°–20° within 15 minutes and the mixture is stirred at room temperature for a further 3 hours. After concentration under reduced pressure the residue is partitioned between ice-water and ethyl acetate. The organic phase, dried over sodium sulphate, is evaporated and the residual oil is chromatographed on 100 g of silica gel with ethyl acetate as the elution agent. The 2-[3-(N-benzyloxycarbonylmethylamino)propyl]-1-methyl-4,5-diphenylimidazole (6.4 g of oil) obtained is dissolved in 300 ml of methanol and hydrogenated at room temperature and normal pressure in the presence of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual manner, is chromatographed on 70 g of silica gel with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 2.95 g (64%) of 1-methyl-2-[3-(methylamino)propyl]-4.5-diphenylimidazole as a thick oil.

EXAMPLE 34

In an analoqous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[3-(methylamino)propyl]-4,5-diphenylimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m p. 160°–164°, as a colourless crystalline powder.

EXAMPLE 35

In an analogous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[4-[(methylamino)methyl]benzyl]-1-methyl-benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(1-methyl-2-benzimdazolyl)methyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 130°-134°, as an almost colourless crystalline powder.

The 2-[4-[(methylamino)methyl]benzyl]-1-methylbenzimidazole used as the starting material was prepared as follows:

A mixture of 30 g (0.277 mol) of o-phenylenediamine and 150 g of polyphosphoric acid ester (ppE) is heated to 120°. When the diamine has dissolved, 33 g (0.205 mol) of p-cyanophenylacetic acid are added thereto in one portion and the mixture is heated to 120° for a further 20 minules. After cooling to room temperature the viscous mass is treated with about 1 l of water and made weakly basic with solid sodium hydrogen carbonate. The mixture is extracted with methylene chloride and the extract is washed with water, dried over sodium sulphate and evaporated to dryness. Recrystallization of the residue from methylene chloride/ethyl acetate gives 29 g (60%) of 2-(p-cyanobenzyl)benzimidazole, m.p. 201°-203°, as a colourless crystalline powder.

A solution of 21.9 g of 2-(p-cyanobenzyl)benzimidazole in a mixture of 140 ml of methanol and 140 ml of liquid ammonia is hydrogenated at room temperature and 30 bar in the presence of 5 g of Raney-nickel. The product, isolated in the usual manner, is chromatographed on 400 g of silica gel with methanol as the elution agent. The homogeneous fractions give, after evaporation and trituration of the residue with ether, 14.7 g (66%) of 2-[p-(aminomethyl)benzyl]benzimidazole, m.p. 133°-136°, as a pale brown crystalline powder.

A solution of 9.2 g (0.04 mol) of 2-[p-(aminomethyl)-benzyl]benzimidazole and 8.4 ml (0.06 mol) of benzyl chloroformate in 80 ml of dimethylformamide is treated with 10 g of finely ground dry potassium carbonate and thereupon stirred intensively at room temperature for 30 minutes. 12 ml (0.08 mol) of 1,8-diazabicyclo[5.-4,O]undec-7-ene (DBU) are then added thereto and the mixture is stirred at room temperature for a further 30 minutes. The inorganic salts are filtered off, rinsed with methylene chloride and the filtrate is concentrated to dryness under reduced pressure. The oily residue is chromatographed on 600 g of silica gel firstly with methylene chloride/ethyl acetate (4:1) and then with chloroform/ethanol (9:1) as the elution agent. The fractions eluted with chloroform/ethanol give, after evaporation and trituration with ethyl acetate, 10.8 g (73%) of benzyl [4-[2-(benzimidazolyl)methyl] benzyl]carbamate, m.p. 190°-194°, as a colourless crystalline powder.

A solution of 8.9 g (0.024 mol) of benzyl [4-[2-(benzimidazolyl)methyl]benzyl]carbamate in 210 ml of dimethylformamide is treated at 15°-20° under argon with 0.056 mol of sodium hydride (2.5 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 7.4 ml (0 12 mol) of methyl iodide in 22 ml of dimethylformamide is added thereto at 15°-20° within 20 minutes and the mixture is stirred at room temperature for a further 10 minutes. After concentration under reduced pressure the residue is partitioned between ice-water and ethyl acetate. The organic phase. dried over sodium sulphate, is evaporated and the residual oil is chromatographed on 300 g of silica gel with methylene chloride/ethyl acetate (1:1) as the elution agent. The first fractions which are eluted homogeneous yield, after evaporation and trituration with ether, 4.5 g (45%) of benzyl [4-[1-(1-methyl-2-benzimidazolyl)ethyl]benzyl]methylcarbamate, m.p. 131°-133°, as a colourless crystalline powder. The following fractions which are eluted homogeneous give, after concentration, 3.5 g (37%) of benzyl [4-[(1-methyl-2-benzimidazolyl)methyl]benzyl]methylcarbamate as a viscous oil.

3.5 g of benzyl [4-[(1-methyl-2-benzimidazolyl)methyl]benzyl]methylcarbamate are dissolved in 600 ml of methanol and hydrogenated at room temperature and normal pressure after the addition of 1 g of 5% palladium-on-active charcoal. The product. isolated in the usual manner, is chromatographed on 150 g of silica gel with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 2.1 g (90%) of 2-[4-[(methylamino)methyl]benzyl]-1-methylbenzimidazole as a thick oil.

EXAMPLE 36

In an analogous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[1-[4-[(methylamino)methyl]phenyl]ethyl]-1-methyl-benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[1-(1-methyl-2-benzimidazolyl)ethyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride (mixture of 2 epimers), m.p. 95°-105°, as an almost colourless crystalline powder.

The 2-[1-[4-[(methylamino)methyl]phenyl]ethyl]-1-methylbenzimidazole used as the starting material was prepared in an analogous manner to that given in Example 35 by hydrogenating benzyl [4-[1-(1-methyl-2-benzimidazolyl)ethyl]benzyl]methylcarbamate.

EXAMPLE 37

In an analogous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[4-[(methylamino)methyl]benzyl]-benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(2-benzimidazolyl)methyl]benzyl]-methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 146°-150°, as an almost colourless crystalline powder.

The 2-[4-[(methylamino)methyl]benzyl]benzimidazole used as the starting material was prepared as follows:

6.6 g (0.028 mol) of 2-(p-cyanobenzyl)benzimidazole are heated to reflux for 2 hours in 110 ml of 1N sodium hydroxide solution. The solution obtained is cooled and extracted twice with 100 ml of ethyl acetate and twice with 100 ml of methylene chloride. The aqueous phase is adjusted to pH 6.0 with 2N hydrochloric acid and left to stand in an ice-bath for 30 minutes. The precipitate is filtered off under suction and washed with ether. There are obtained 5.8 g (83%) of p-[(2-benzimidazolyl)methyl]benzoic acid, m.p. 265°-267°, as a colourless powder.

2.8 ml of butyl chloroformate are added dropwise at −5° to a solution of 5.0 g (0.020 mol) of p-[(2-benzimidazolyl)methyl]benzoic acid and 2.8 ml (0.020 mol) of triethylamine in 68 ml of dimethylformamide. After stirring at 0°–5° for 30 minutes 1.32 g (0.020 mol) of methylamine hydrochloride and 2.8 ml (0.020 mol) of triethylamine in 28 ml of dimethylformamide and 1.4 ml of water are added. The temperature is then left to rise to room temperature and the mixture is stirred for a further 18 hours. After concentration under reduced pressure the residue is chromatographed on 400 g of silica gel with chloroform/ethanol (4:1) as the elution agent. The uniform fractions give 2.0 g (38%) of N-methyl-p-[(2-benzimidazolyl)methyl]benzamide, m.p. 250°–255° (dec.), as a colourless powder.

1.98 g (0.0075 mol) of N-methyl-p-[(2-benzimidazolyl)methyl]benzamide are added portionwise to a stirred suspension of 0.58 g (0.0075 mol) of lithium aluminium hydride in 40 ml of tetrahydrofuran and subsequently heated to reflux for 4 hours. At 5°–10° there are added dropwise 1.5 ml of water, then 2.3 ml of a 10% solution of potassium hydroxide and again 1.5 ml of water. The precipitate is filtered off and boiled three times with 20 ml of tetrahydrofuran each time. The combined filtrates are washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness under reduced pressure. The residue is chromatographed on 150 g of silica gel with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 1.58 g (84%) of 2-[4-[(methylamino)methyl]benzyl]benzimidazole, m.p. 157°–160°, as a colourless crystalline powder.

EXAMPLE 38

In an analoqous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-1isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[trans-4-[(methylamino)methyl]cyclohexyl]benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[trans-4-(2-benzimidazolyl)cyclohexyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 150°–153°, as a colourless crystalline powder.

The 2-[trans-4-[(methylamino)methyl]cyclohexyl]-benzimidazole used as the starting material was prepared as follows:

A solutionoof 20.3 g (0.07 mol) of trans-4-(N-benzyloxycarbonyl-aminomethyl)cyclohexanecarboxylic acid in 380 ml of dimethylformamide is treated at 15°–20° under argon with 0.21 mol of sodium hydride (9.35 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 17.5 ml (0.28 mol) of methyl iodide in 20 ml of dimethylformamide is added thereto at 25°–30° within 20 minutes and the mixture is stirred at 70° for a further 1 hour. After concentration under reduced pressure the residue is partitioned between water and methylene chloride. The organic phase is evaporated and the residual oil is dissolved in a mixture of 350 ml of ethanol and 350 ml of 1N sodium hydroxide solution. The mixture is heated to reflux for 1 hour, cooled and poured into 700 ml of ice-water The solution is extracted with ethyl acetate and then acidified with 6N hydrochloric acid. The liberated acid is extracted with methylene chloride and the extract is dried over sodium sulphate and evaporated. The residual oil is chromatographed on 270 g of silica gel with a mixture of methylene chloride-/ethyl acetate (4:1) as the elution agent. There are obtained 13.6 g (64%) of trans-4-(N-benzyloxycarbonyl-N-methyl-aminomethyl)cyclohexanecarboxylic acid as a thick oil.

A solution of 13.6 g (0.044 mol) of trans-4-(N-benzyloxycarbonyl-N-methyl-aminomethyl)cyclohexanecarboxylic acid and 9.5 ml (0.068 mol) of triethylamine in 110 ml of tetrahydrofuran is treated at −15° within 30 minutes with 6.5 ml (0.049 mol) of isobutyl chloroformate. A solution of 5.8 g (0.053 mol) of o-phenylenediamine is then added dropwise at −15° within 45 minutes. The mixture is stirred at room temperature for 1 hour and left to stand for 20 hours. After concentration under reduced pressure the residue is partitioned between water and ethyl acetate and the organic phase is washed with a 5% solution of sodium hydrogen carbonate, then with a saturated aqueous solution of sodium chloride and finally with water. The solution, dried over magnesium sulphate, is evaporated and triturated with ether. The solid product obtained (9.3 g) is dissolved in 200 ml of toluene, 3 g of p-toluenesulphonic acid are added thereto and the mixture is heated to reflux for 4 hours with a water separator. The solution is cooled, washed with a 2N sodium carbonate solution and a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to dryness under reduced pressure. The solid residue is recrystallized from ethyl acetate. There are obtained 5.6 g of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate, m.p. 146°–148°, as a colourless crystalline powder. After chromatography on 250 g of silica gel with ethyl acetate/methylene chloride (9:1) as the elution agent the mother liquor gives a further 1.1 g of the same product, m.p. 146°–148°. Total yield: 6.7 g (40%).

6.0 g of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate are dissolved in 600 ml of ethanol and hydrogenated at room temperature and normal pressure after the addition of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual manner, is recrystallized from methylene chloride/ether. There are obtained 3.0 g (78%) of 2-[trans-4-[(methylamino)methyl]cyclohexyl]benzimidazole, m.p. 232°–235°, as a colourless crystalline powder.

EXAMPLE 39

In an analogous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted firstly with 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 148°–152°, as a colourless crystalline powder.

The 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole used as the starting material was prepared as follows:

A solution of 7.2 g (0.019 mol) of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate in 160 ml of dimethylformamide is treated at 15°–20° under argon with 0.023 mol of sodium hydride (1.0 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 2.3 ml (0.038 mol) of methyl iodide in 10 ml of di-

methylformamide is added thereto at 15°–20° within 15 minutes and the mixture is stirred at room temperature for a further 3 hours. After concentration under reduced pressure the residue is partitioned between ice-water and ethyl acetate. The organic phase, dried over sodium sulphate, is evaporated and the solid residue is recrystallized from ethyl acetate/ether. There are obtained 5.9 g (79%) of benzyl [[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate, m.p. 141°–142°, as a colourless crystalline powder.

5.9 g of benzyl [[trans-4-(1-methyl-2-benzimidazolyl)-cyclohexyl]methyl]methylcarbamate are dissolved in 600 ml of ethanol and hydrogenated at room temperature and normal pressure after the addition of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual manner, is chromatographed on 250 g of silica gel firstly with methylene chloride/methanol (1:1) and then with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 3.3 g (85%) of 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole as a thick oil.

EXAMPLE 40

In an analogous manner to that described in Example 7, by reacting 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and 3,4-dihydro-4-methyl-1-[4-(methylamino)butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione there is obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2.5-(1H)-dione. MS: M+ 509.

In an analogous manner to that described above, starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthyl)ethyl p-toluenesulphonate and (S)-6-chloro-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5.11-(10H)-dione there was prepared (S)-6-chloro-10-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-(10H)-dione, MS: M+ 570.

The 3,4-dihydro-4-methyl-1-[4-(methylamino)butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione used as the starting material was prepared as follows:

10 g (40 mmol) of 4-[1-(benzyloxy)-N-methylformamido]butyric acid are dissolved in 200 ml of ethanol and treated with 1 ml of concentrated sulphuric acid. Thereafter, the reaction mixture is heated to reflux for 4 hours and the solvent is subsequently evaporated off. The reaction product is then extracted with methylene chloride/saturated sodium bicarbonate solution. After drying and evaporation of the extract there are obtained 9.24 g of a brown oil which is dissolved in 200 ml of tetrahydrofuran, treated with 7.1 ml of 10M boron methylsulphide complex and heated to reflux for 2 hours. Thereafter, the reaction mixture is left to stand at room temperature overnight and then sufficient methanol is slowly added thereto so that gas evolution no longer occurs. In this manner there is obtained a clear solution which is evaporated. The residue obtained (8.09 g) is chromatographed on silica gel with a 1:1 mixture of ethyl acetate and hexane, whereby there are obtained 6.82 g (72%) of benzyl (4-hydroxybutyl)methylcarbamate which is used directly in the next step.

6.75 g (28.4 mmol) of the carbamate obtained above and 10.0 g (52.5 mmol) of p-toluenesulphonyl chloride are dissolved in 25 ml of pyridine at 0°. After standing for 6 hours the mixture is added to ice and extracted with ether. The ether extract is washed with 4N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried and evaporated. In this manner there are obtained 9.38 g (84%) of a yellowish oil of benzyl methyl [4-[(p-toluenesulphonyl)oxy]butyl]-carbamate which is processed directly.

1.9 g (10 mmol) of 4-methyl-3H-1,4-benzodiazepine-2,5-(1H,4H)-dione are dissolved in 20 ml of dimethylformamide and added to a suspension of 430 mg (10 mmol) of 55% sodium hydride in 50 ml of dimethylformamide. 30 minutes after the addition a solution of 3.91 g (10 mmol) of benzyl methyl [4-[(p-toluenesulphonyl)oxy]butyl]carbamate in 20 ml of dimethylformamide is added and the whole reaction mixture is stirred at room temperature for 20 hours. Thereafter, the solvent is evaporated under reduced pressure at 50° and water is subsequently added. After two-fold extraction with methylene chloride the solvent is again evaporated and the residue is chromatographed on silica gel with a 20:1 mixture of methylene chloride and methanol, whereby there are obtained 3.92 g (95.8%) of benzyl methyl [4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-yl)butyl]carbamate, MS: M+ 409.

The above carbamate is converted in an analogous manner to that described in Example 7, last paragraph, into the desired 3,4-dihydro-4-methyl-1-[4-(methylamino)butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione which is used directly in the next step.

In an analogous manner to that described above, starting from benzyl methyl-[4-[(p-toluenesulphonyl-)oxy]butyl]carbamate by reaction with the corresponding benzodiazepine there was prepared (S)-6-chloro-1,2,3,11a-tetrahydro-10-[4-(methylamino)butyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-(10H)-dione.

EXAMPLE 41

The following compounds were prepared in an analogous manner to that described in Example 8 by methoxy-acetylating the corresponding hydroxy derivatives:

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-yl)butyl]methylamino]ethyl]-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_{589}^{20} = +28.2°$ (c=0.5%; methanol);

[1S,2S]-2-[2-[[4-[(S)-6-chloro-2,3,11,11a-tetrahydro-5.1-1-dioxo-1H-pyrrolo[2.1-c][1.4]benzodiazepin-10(5H)-yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride, $[\alpha]_{589}^{20} = +215.2°$ (c=0.5%; methanol).

EXAMPLE A

Tablets

	Composition:	
(1)	2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	75 mg
(2)	Lactose powdered	135 mg
(3)	Maize starch white	55 mg
(4)	Povidone K 30 (polyvinylpyrrolidone)	15 mg
(5)	Maize starch white	15 mg
(6)	Talc	3 mg
(7)	Magnesium stearate	2 mg
	Tablet weight	300 mg

Manufacturing procedure:

1-3 are mixed intensively. The mixture is thereafter moistened with an aqueous solution of 4 and kneaded, and the resulting mass is granuolated, dried and sieved. The granulate is mixed with 5-7 and pressed to tablets of suitable size.

EXAMPLE B

Tablets		
Composition:		
(1) 2-[2-[[3-(2-Benzimidazolyl)-propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	75 mg	60 mg
(2) Lactose powdered	100 mg	100 mg
(3) Maize starch	60 mg	60 mg
(4) Povidone K 30 (polyvinylpyrrolidone)	5 mg	5 mg
(5) Maize starch	15 mg	15 mg
(6) Sodium carboxymethylstarch	5 mg	5 mg
(7) Talc	3 mg	3 mg
(8) Magnesium stearate	2 mg	2 mg
Tablet weight	265 mg	250 mg

Manufacutring procedure:

1-3 mixed intensively. The mixture is thereafter moistened with an aqueous solution of 4 and kneaded, and the resulitng mass is granulated, dried and sieved. The granulate is mixed with 5-8 and pressed to tablets of suitable size.

EXAMPLE C

Tablets		
Composition:		
(1) 2-[2-[[3-(2-Benzimidazolyl)-propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	75 mg	90 mg
(2) Lactose powdered	46 mg	46 mg
(3) Cellulose microcrystalline	60 mg	60 mg
(4) Povidone K 30 (polyvinylpyrrolidone)	10 mg	10 mg
(5) Sodium carboxymethylstarch	4 mg	4 mg
(6) Talc	3 mg	3 mg
(7) Magnesium stearate	2 mg	2 mg
Tablet weight	200 mg	215 mg

Manufacturing procedure:

1-3 are mixed intensively. The mixture is therafter moistened with an aqueous solution of 4 and kneaded, and the resulting mass is granulated, dried and sieved. The granulate is mixed with 5-7 and pressed to tablets of suitable size.

EXAMPLE D

Capsules	
Composition:	
(1) 2-[2-[[3-(2-Benzimidazolyl)propyl]methyl-amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	75 mg
(2) Lactose crystalline	100 mg
(3) Maize starch white	20 mg
(4) Talc	9 mg
(5) Magnesium stearate	1 mg
Capsule fill weight	205 mg

Manufacturing procedure:

The active substance is mixed intensively with the lactose. This mixture is thereafter admixed with the maize starch, the talc and the magnesium stearate, and the mixtture is filled into capsules of suitable size.

EXAMPLE E

Capsules	
Composition:	
(1) 2-[2-[[3-(2-Benzimidazolyl)propyl]methyl-amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	75 mg
(2) Cellulose microcrystalline	100 mg
(3) Sodium carboxymethylstarch	5 mg
(4) Talc	9 mg
(5) Magnesium stearate	1 mg
Capsule fill weight	190 mg

Manufacturing procedure:

The active substance is mixed intesnively with the cellulose. This mixture is thereafter admixed with the odium carboxymethylstarch, the talc and the magniesium stearate, and the mixture is filled into capsules of suitable size.

EXAMPLE F

Injection solution	1 ml
2-[2-[[3-(2-Benzimidazolyl)propyl]methyl-amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate hydrochloride	8 mg
Sodium chloride crystalline pure	8.5 mg
Water for injection ad	1 ml

EXAMPLE G

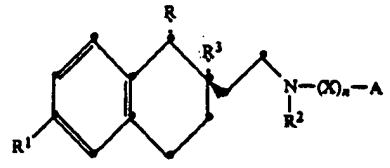
When the procedures described in Examples A-F are followed. tablets, capsules and injection preparations can be manufactured from the following, likewise preferred, compounds and their pharmaceutically usable salts:

[1S,2S]-2-[2-[[3-(2-benzyimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride,

[1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride.

We claim:

1. A compound of the formula



I

wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1-C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy, lower-alkylaminocarbonyloxy; or arylaminocarbonyloxy or aryl-lower-alklaminocarbonyloxy, wherein aryl is phenyl or phenyl mono- or multiplysubstituted by halo-

gen, trifluoromethyl, lower-alkyl, lower-alkoxy, nitro or amino; X is C_1–C_{18}-alkylene which can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group wherein the substituents are selected from the group consisting of lower alkyl and phenyl; or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo-[4,5c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrol[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl wherein the substituents are selected from the group consisting of C_1–C_{12}-alkyl, phenylloweralkyl, halo, morpholinoethyl and pyridylmethyl and wherein the last two of said heterocycles may be partially hydrogenated; and n is number 0 or 1, in the form of a racemate or an optical antipode, an N-oxide, or a pharmaceutically usable acid addition salt thereof.

2. A compound in accordance with claim 1, wherein R is isopropyl.

3. A compound in accordance with claim 2, wherein R^3 is hydroxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy or lower-alkylaminocarbonyloxy.

4. A compound in accordance with claim 3, wherein R^3 is isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy.

5. A compound in accordance with claim 1, wherein n is the number 1.

6. A compound in accordance with claim 1, wherein R^1 is fluorine.

7. A compound in accordance with claim 1, wherein R^2 is methyl.

8. A compound in accordance with claim 1, wherein X is C_3–C_7-alkylene.

9. A compound in accordance with claim 8, wherein X is propylene, butylene, pentamethylene or hexamethylene.

10. A compound in accordance with claim 1, wherein A is 2-benzimidazolyl, 2-benzthiazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydro-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl or 1-methyl-4,5-diphenyl-2-imidazolyl.

11. A compound in accordance with claim 10, wherein A is 2-benzimidazolyl or 2-benzthiazolyl.

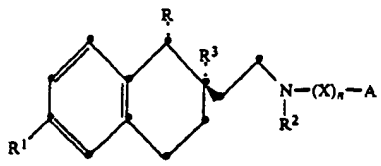
12. A compound in accordance with claim 1, wherein R is isopropyl, R^3 is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy, R^1 is fluorine. R^2 is methyl, X is propylene, butylene, pentamethylene or hexamethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

13. A compound in accordance with claim 1, 2-[2-[[3-(2-benzimidaolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate.

14. A compound in accordance with claim 1, [1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2naphthyl methoxyacetate.

15. A compound in accordance with claim 1, [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate.

16. A composition with calcium antagonistic activity comprising a calcium antagonistically effective amount of a compound of the formula



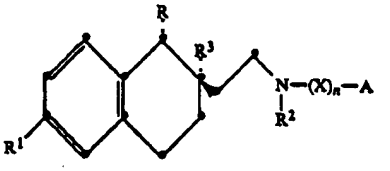
I

wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1–C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alklcarbonyloxy, lower-alkoxy-lower-alkylcarbonyloxy, lower-alkylaminocarbonyloxy; or arylamiocarbonyloxy or aryl-lower-alkylaminocarbonyloxy, wherein aryl is phenyl or phenyl mono- or multiply-substituted by halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, niro or amino; X is C_1–C_{18}-alkylene which can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group wherein the substituents are selected from the group consisting of lower alkyl and phenyl; or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazol[4,5-c]pyridinyl, imidazo-[4,5-c]pyridinyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrol[2,1-c][1,4benzodiazepine-5,11-dion-10-yl wherein the substituents are selected from the group consisting of C_1–C_{12}-alkyl phenylloweralkyl, halo, morpholinoethyl and pyridylmethyl and wherein the last two of said heterocycles may be partially hydrogenated; and n is the number 0 or 1, in the form of a racemate or an optical antipode, an N-oxide, or a pharmaceutically usable acid addition salt thereof, and a pharamaceutically inert excipient.

17. A composition in accordance with claim 16, wherein R is isopropyl, R^3 is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy, R^1 is fluorine, R^2 is methyl, X is propylene, butylene, pentamethylene or hexamethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

18. A composition in accordance with claim 17, wherein the compound of formula I is [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamio]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methyoxyacetate or its racemate.

19. A method of treating or preventing angina petcoris, ischaemia, arrhydthmias, high blood pressure and cardiac insufficiency which comprises administering to a warm-blooded animal in need of such treatment, a calcuim antagonistically effective amount of a compound of the formula



I

wherein R is lower-alkyl, R^1 is halogen, R^2 is C_1–C_{12}-alkyl, R^3 is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower alkylcarbonyloxy, lower-alkylaminocarbonyloxy; or, arylaminocarbonyloxy or aryl-lower-alkylamiocarbonyloxy wherein aryl is phenyl or phenyl mono- or multiplysubstituted by halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, nitro

or amino; X is C_1–C_{18}-alkylene which can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group wherein the substituents are selected from the group consisting of lower alkyl and phenyl; or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, bezthiazoyl, benzodiazepine-2,5-dion-1-yl and pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl wherein the substitutents are selected from the group consisting of C_1–C_{12}-alkyl, phenylloweralkyl, halo, morpholinoethyl and pyridylmethyl and wherein the last two of said heterocycles may be partially hydrogenated; and n is the number 0 or 1, in the form of a racemate or an optical antipode, an N-oxide, or a phamraceutically usable acid addition salt thereof.

20. A method in accordance with claim 19 wherein R is isopropyl, R^3 is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy, R^1 is fluorine, R^2 is methyl, X is propylene, butylene, pentamethylene or hexameethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

21. A method in accordance with claim 20, wherein the compound of formula I is [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate or its racemate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

exhibit (4)

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 11, "and the 106 like" should read --- and the like --- .

Column 8, line 42, "acidiin" should read --- acid in --- .

Column 14, line 63, in the Table, letter G "[1S,2S]-2,6-Fluoro" should read --- [1S,2S]-6-Fluoro --- .

Columns 17-18, line 40, "heated to 0°" should read --- heated to 70° --- .

Column 18, line 52, "[1S,2S]-2-[2755- " should read --- [1S,2S]-2-[2- --- .

Column 19, lines 12-13, "-isopropyl-2ß-naphthalenol" should read --- -isopropyl-2-naphthalenol --- .

Column 19, line 15, "1α-isopropyl-28-naphthyl" should read --- 1α-isopropyl-2ß-naphthyl --- .

Column 20, line 38, "Thereafter." should read --- Thereafter, --- .

Column 21, line 65, "(37.2% of" should read --- (37.2%) of --- .

Column 22, line 4, "of 6997-fluoro" should read --- of 6-fluoro --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 22, line 5, "tetrahydro-2-isopropyl-2-hydroxy" should read --- tetrahydro-2-hydroxy --- .

Column 23, line 34, "an anaoogous manner" should read --- an analogous manner --- .

Column 25, line 22, "water.dried over" should read --- water, dried over --- .

Column 26, line 6, "Thereafter." should read --- Thereafter, --- .

Column 26, line 21, "benzimiaazolinyl]" should read --- benzimidazolinyl- --- .

Column 26, line 58, "1-[6-[[2-[[7S,2S]- " should read --- 1-[6-[[2-[[1S,2S]- --- .

Column 27, line 37, "analoqous" should read --- analogous --- .

Column 28, line 53, "2hydroxy-" should read --- 2-hydroxy- --- .

Column 29, line 47, "analogous" should read --- analogous --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 29, line 47, "lhat" should read --- that --- .

Column 30, line 4, "With" should read --- with --- .

Column 30, line 22, "1.2,3,4-tetrahydro" should read --- 1,2,3,4-tetrahydro --- .

Column 30, line 53, "[4.5-c]" should read --- [4,5-c] --- .

Column 30, line 55, "[4.5-c]" should read --- [4,5-c] --- .

Column 32, line 24, "water." should read --- water, --- .

Column 32, line 44, " (0 005 mol)" should read --- (0.005 mol) --- .

Column 33, line 10, " -4.5-" should read --- -4,5- --- .

Column 33, line 15, "sodium chloride.dried" should read --- sodium chloride, dried --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 33, line 57, " N-methyl-4.5- " should read
--- -N-methyl-4,5- --- .

Column 34, line 55, " -4.5- " should read
--- -4,5- --- .

Column 34, line 59, "analoqous" should read
--- analogous --- .

Column 35, line 17, " (ppE)" should read
--- (PPE) --- .

Column 35, line 21, "minuIes" should read
--- minutes --- .

Column 35, lines 46-47, " [5.4,0] " should read
--- [5.4.0] --- .

Column 35, lines 65-66, "0 12mol)" should read
--- (0.12) --- .

Column 36, line 3, "The organic phase." should read
--- The organic phase, --- .

Column 36, line 19, "The product.isolated" should read
--- The product, isolated --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37, line 36, "analoqous" should read --- analogous --- .

Column 37, line 49, "A solutionof" should read --- A solution of --- .

Column 37, line 64, "ice-water The" should read --- ice-water. The --- .

Column 39, line 15, "The product.isolated in" should read --- The product, isolated in --- .

Column 39, line 31, " -1,4-benzodiazepine-2.5-(1H)- " should read --- -1,4-benzodiazepine-2,5-(1H)- --- .

Column 39, line 37, " [1,4]benzodiazepine-5.11-(10H) " should read --- [1,4]benzodiazepine-5,11-(10H) --- .

Column 40, lines 47-48, " -5.11- " should read --- -5,11- --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 40, line 48, " [2.1-c][1.4] " should read --- [2,1-c][1,4] --- .

Column 41, line 3, " granuolated " should read --- granulated --- .

Column 41, line 25, "Manufacutring" should read --- Manufacturing --- .

Column 41, line 28, "resulitng" should read --- resulting --- .

Column 41, line 49, "therafter" should read --- thereafter --- .

Column 42, line 5, "mixtture" should read --- mixture --- .

Column 42, line 22, "intesnively" should read --- intensively --- .

Column 42, line 24, "odium" should read --- sodium --- .

Column 42, lines 24-25, "magniesium" shoùld read --- magnesium --- .

Column 42, line 41, "followed.tablets" should read --- followed, tablets --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 42, line 67, "alklaminocarbonyloxy" should read --- alkylamino-carbonyloxy --- .

Column 42, line 68, "multiplysubstituted" should read --- multiply-substituted --- .

Column 43, line 10, "[4,5c]" should read --- [4,5-c] --- .

Column 43, line 55, " (2-benzimidaolyl)" should read --- -(2-benzimidazolyl) --- .

Column 44, lines 11-12, "lower-alklcarbonyloxy" should read --- -lower-alkyl-carbonyloxy --- .

Column 44, line 13, "arylamio-carbonyloxy" should read --- arylaminocarbonyloxy --- .

Column 44, line 17, "niro" should read --- nitro --- .

Column 44, lines 18-19, "intrrupted" should read --- interrupted --- .

Column 44, line 25, "pyridinyl" should read --- pyridinonyl --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 44, lines 27-28, "[1,4benzodiazepine-" should read ---[1,4]benzodiazepine---.

Column 44, line 44, "(2-benzimidazolyl)propyl]methyl -amio]ethyl " should read ---(2-benzimidazolyl)propyl] methyl- amino]ethyl --- .

Column 44, lines 47-48, "petcoris" should read --- pectoris --- .

Column 44, line 48, "arrhydthmias" should read --- arrhythmias --- .

Column 44, line 51, "calcuim" should read --- calcium --- .

Column 44, line 66, "aryl-lower-alkylamio-carbonyloxy" should read ---aryl-lower-alkyl-aminocarbonyloxy--- .

Column 44, line 67, "multiplysubstituted" should read --- multiply-substituted --- .

Column 45, line 9, "bezthiazoyl" should read --- benzthiazolyl --- .

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,605
DATED : February 28, 1989
INVENTOR(S) : Quirico Branca, Roland Juanin, Hans Peter Märki, Fränz Marti, Henri Ramuz

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 46, line 2, "phamraceutically" should read --- pharmaceutically --- .

Column 46, line 4, "Claim 19 wherein" should read --- Claim 19, wherein --- .

Column 46, line 8, "hexameethylene" should read --- hexamethylene --- .

Signed and Sealed this

Seventeenth Day of October, 1995

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000151

75M7/0724

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,808,605	184	1990	----	07/119,114	02/28/89	11/10/87	08	NO	PAID

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If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	4029/6

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV 4-88)

MARION MERRELL DOW INC.

exhibit (5)

Marion Merrell Dow Inc.
MAIL P.O. Box 9627
Kansas City, Missouri 64134-0627
Telephone 816 966-5000

June 24, 1992

Central Document Room
Center for Drugs and Biologics
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

SUBJECT: IND
RO-40-5967

Amendment 000:
Initial Submission

Gentlemen:

In accordance with the Federal Food, Drug and Cosmetic Act and pursuant regulations, we are submitting in triplicate an Investigational New Drug Application for RO-40-5967. This submission consists of 12 volumes.

Marion Merrell Dow Inc. will be conducting clinical trials to determine the safety and efficacy of RO-40 in treatment of hypertension and angina.

Marion Merrell Dow Inc. considers the data submitted with this application to be a trade secret and protected from disclosure under the provisions of 21 CFR §312.130 and §314.430.

Any questions concerning this Investigational New Drug Application should be directed to :

J. Michael Nicholas, Ph.D. 816/966-5720
- or -
Diane J. Seif, MBA 816/966-7927
MARION MERRELL DOW INC.
P.O. Box 9627
Kansas City, MO 64134-0627

Sincerely,

MARION MERRELL DOW INC.

Judith A. Hemberger

Judith A. Hemberger, Ph.D.
Vice President
Global Regulatory and Medical Affairs

JAH/kal

Attachments

c:\wp51\jmn\r0-40

exhibit (6)

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-812-3688
Fax 201-812-3700/3554

March 8, 1996

Food and Drug Administration
Central Document Room
Center for Drug Evaluation and Research
ATTEN.: DOCUMENT CONTROL ROOM #214
12420 Parklawn Drive
Rockville, MD 20852

Gentlemen:

Re: NDA 20-689
Posicor™ (mibefradil dihydrochloride) Tablets
Original New Drug Application

In accordance with 21CFR Part 314.50, Hoffmann-La Roche Inc. herewith submits an original New Drug Application (NDA 20-689) for Posicor (mibefradil dihydrochloride) tablets, a structurally new calcium antagonist for use in the treatment of hypertension and chronic stable angina pectoris. Posicor has been the subject of IND 39,901 sponsored by Hoffmann-La Roche Inc., Nutley, New Jersey, and has been jointly developed with Roche Products, Ltd., Welwyn Garden City, United Kingdom and F. Hoffmann-La Roche and Company, Ltd., Basel, Switzerland.

The information submitted in this NDA in support of the safety and efficacy of Posicor has been derived from studies conducted under IND 39,901 and from foreign preclinical and clinical non-IND studies conducted under the auspices of Roche Products, Ltd., Welwyn Garden City, United Kingdom and F. Hoffmann-La Roche and Company, Ltd., Basel, Switzerland. Posicor is also being studied for use in the treatment of congestive heart failure in a three-year morbidity/mortality study (MACH I) under IND 45,728. This study is projected to finish mid-1998, and an NDA is planned for December 1998.

Roche

This NDA documents the safety and effectiveness of Posicor for two indications, the treatment of hypertension and chronic stable angina pectoris. The data presented was derived from a total 4,279 who were treated with Posicor for periods of one day to longer than one year. Of these patients, 2,194 were treated with Posicor in the hypertension program in nine controlled, double-blind, randomized, parallel group studies (4 placebo-controlled, 2 active and placebo-controlled, 3 active-controlled) and one open-label, long-term study, and 1,236 patients were treated with Posicor in the chronic stable angina pectoris program in six controlled, double-blind, randomized, parallel group design studies (five placebo-controlled, one active-controlled, randomized, placebo-controlled withdrawal study) and, one open label, long-term safety study. Additionally, 607 subjects and patients in the clinical pharmacology program and 242 patients with congestive heart failure were treated with Posicor.

The Integrated Summary of Safety contains all safety data from patients for which case report forms were available as of April 7, 1995. Additionally, all serious adverse experiences and deaths are reported through September 30, 1995.

Section 3 of this NDA provides for the manufacture of the drug substance, mibefradil dihydrochloride, at Fabbrica Italiana Sintetici S.P.A., Vicenza, Italy. The finished dosage forms are to be prepared by Hoffmann-La Roche Inc., Nutley, New Jersey. As an aid to the CMC and biopharmaceutics reviewers, an integrated summary has been prepared covering formulation development from investigational to proposed market formulations, bioequivalent linkage of formulations, and identification of drug formulations used in clinical investigations. This summary is submitted both in Section 3 as Volumes 9 and 10 and Section 6 as Volumes 224 and 225.

The NDA incorporates the various suggestions of the Division as discussed in our January 29, 1993, End of Phase II meeting, May 18, 1995, pre-NDA meeting, and our November 16, 1995, pre-NDA Chemistry, Manufacturing and Controls meeting.

At present, two toxicology studies are ongoing: A 78-week time-course study in rats comparing the effect of the administration of mibefradil dihydrochloride by dietary admix and oral gavage on the development of periodonitis and a repeat of the two-year rat carcinogenicity study using oral gavage as the means for drug administration. As agreed with the Division, this NDA is being filed with 12-month and 10-month interim data from the 78-week time-course and repeat carcinogenicity studies, respectively. Final study results, as agreed, will be submitted to this NDA without impact on the 12-month user fee review clock as amendments in July 1996 for the time-course study and November 1996 for the repeat carcinogenicity study.

Roche

Division of Cardio-Renal Drug Products
March 8, 1996
Page Three

An identical field copy containing a completed Form 356h, Section 2 (Application Summary) and Section 3 (CMC) of this NDA is being submitted simultaneously to the Newark District Office of the FDA. The undersigned hereby certifies that the copy submitted to the District Office is a true copy of that submitted to the Division of Cardio-Renal Drug Products.

This submission consists of an archival (749 volumes) and a review copy. In addition, a CANDA consisting of textural, image, graphical and statistical subsystems is being provided with this NDA.

This NDA is organized as follows:

Two desk copies of the Table of Contents for the entire NDA (Section 1) and the NDA Summary (Section 2) are being provided directly to Mr. David Roeder, CSO in the Division of Cardio-Renal Drug Products.

Roche

We understand that this New Drug Application and all information contained herein, unless otherwise made public by Hoffmann-La Roche Inc., is CONFIDENTIAL and will remain so subsequent to approval of the NDA for this drug. If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials contained in this NDA should be made to any member of the public, we expect that because of the importance of maintaining confidentiality of these materials to Hoffmann-La Roche Inc., you will first consult with us on the issue of disclosure.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

HOFFMANN-LA ROCHE INC.

Rudolph W. Lucek
Associate Director
Drug Regulatory Affairs

RWL/dd
HLR 1996-414

Enclosures: Form FDA 356h
Archival: 749 Volumes
Review: 683 Volumes

Desk Copies: Mr. David Roeder, CSO
2 copies of each Section 1 and Section 2

Posicor IND 39,901

Filing Date	Name	Type/ Number	Description
6/24/92	mibefradil	IND 39,901	Mibefradil (Ro 40-5967) for the Treatment of Hypertension and Chronic Stable Angina Pectoris. Original submission consisting of I2 volumes.
6/26/92	mibefradil	IND 39,901	FDA Letter: ACKNOW Receipt/IND/FDA Acknowledgment of Receipt/Original IND submitted on 6/24/92. Date of Receipt is 6/25/92
7/16/92	mibefradil	IND 39,901	Serial # 001: Protocol Amendment/ Two New Protocols, RA-BP-1191 and RA-DT-3791. New Investigator for both of these Protocols. Study Numbers are the same as Protocol Numbers.
7/22/92	mibefradil	IND 39,901	Telcon:FDA had questions regarding the IND and on the Product.
8/5/92	mibefradil	IND 39,901	Serial No. 002: Response to questions concerning case report forms and Protocols ROPRC-002 and ROPR0003.
8/7/92	mibefradil	IND 39,901	FDA called with concerns over ADE that had previously been reported for RO-40-5967.
		39,901	FDA called regarding the preclinical data for RO-40-5967.
8/17/92	mibefradil	IND 39,901	FDA called in reference to 8/5/92 Response to FDA questions. FDA provided perspective and advice for Lab Assessments in ROPR0002 and data provided from previous studies.
8/20/92	mibefradil	IND 39,901	Serial #003: Protocol Amendment/Protocol Addendum dated 6/17/92 for Protocol ROPR0002, Study No. ROST0002; New Investigators; ROST0034, 0035, 0036, 0038, 0042, 0045, 0046, 0048, 0049, 0051.
8/25/92	mibefradil	IND 39,901	FDA call regarding 8/20 submission, said the Serial # should be 003 and records should be corrected.
8/28/92	mibefradil	IND 39,901	Call to FDA to set up a conference call.
9/1/92	mibefradil	IND 39,901	Serial # 004: FDA requested info/ pages from IND submitted to help clarify recent protocol discussions which took place on Wednesday, 9/2/92.
		39,901	MMD called to determine the status of several projects with the cardio-renal division. Copy of data from 20-062:920901.
9/2/92	mibefradil	IND 39,901	Held a conference call to address the comments made earlier by FDA concerning certain measurements.
9/8/92	mibefradil	IND 39,901	MMD called to inform the FDA that HPB has been put on hold on the beta-blocker study.
		39,901	Serial #005: FDA requested info/material sent in request to conference call on 9/2/92.
9/21/92	mibefradil	IND 39,901	Serial #006: Protocol Amendment/ New Protocol: ROPR0008; New Investigators ROST0037, ROST0041, ROST0052, ROST0054, ROST0067; New Subinvestigator, MD-ROST0051, ROPR0003.
9/23/92	mibefradil	IND 39,901	FAX/Ltr.-recommendations/ Ltr./FDA making requests and recommendations before continuing review.
9/30/92	mibefradil	IND 39,901	Serial #007/Protocol/Mfg. Info./Submit Protocol information for ROPR0003 and Chem MFG & controls info. on 50MG size tablet formulation.
10/8/92	mibefradil	IND 39,901	Serial #008: Protocol Amendment/ New Protocol: ROPR0011; Addendum for ROPROO11; New Investigator: ROST0094.

*Not all communications from FDA to Roche listed in this Exhibit 7.

10/21/92	mibefradil	IND 39,901	Serial #009: Protocol Amendment/New Protocol: ROPR0004, New investigator: ROST0113. Additional site for ROST0041.
10/27/92	mibefradil	IND 39,901	FDA called with questions regarding RO-40 and submission of 10/21 submission 009.
11/3/92	mibefradil	IND 39,901	Talked to FDA regarding ROPR0004, Angina study with concomitant beta blocker.
11/6/92	mibefradil	IND 39,901	Serial #011: Gen. correspond./ info. sent concerning Interactions on this compound and safety information from Roche on their dose response trial in angina patients.
11/11/92	mibefradil	IND 39,901	Serial #010: Protocol Amendment/ New investigators: ROST0040; ROST0047; ROST0057.
11/13/92	mibefradil	IND 39,901	Talked to FDA concerning the submission which described the Canadian experience and the info. from the Roche dose-response trial.
11/19/92	mibefradil	IND 39,901	Status of clinical programs was discussed with the FDA.
		39,901	Serial #012/ Authorize Hoffmann-La Roche to communicate with cardio-renal division concerning this IND for Ro-40-5967.
11/23/92	mibefradil	IND 39,901	Letter/Fax: Partial clin. hold/ Fax asking to respond to questions about Protocol ROPR0004 transferred 12/10/92 to Roche.
11/24/92	mibefradil	IND 39,901	FDA called to inform us that the medical reviewer had placed a partial clinical hold on the RO-40-5967 program.
12/4/92	mibefradil	IND 39,901	Letter from FDA saying can not initiate study because of deficiencies.
12/10/92	mibefradil	IND 39,901	Serial #013: Transfer of IND to Hoffmann-La Roche Inc.
12/10/92	mibefradil	IND 39,901	Informed FDA that HLR has accepted ownership of IND 39,901 from Marion Merrell Dow Inc. During transition phase from 12/10/92 to 4/1/93, Marion Merrell Dow and HLR will share responsibility for ongoing clinical studies.
1/15/93	mibefradil	IND 39,901	Confirmation of End of Phase II meeting scheduled on 1/29/93, with members of the Agency to review proposed Phase III development program for establishing the efficacy and safety of Ro 40-5967, a calcium channel blocker, for use in the treatment of chronic stable angina.
2/10/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators/New Subinvestigators in Protocol ROPR0008.
2/18/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol ROPR0008, and Protocol ROPR0011. New Medical/Safety Monitor.
3/4/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol ROPR0011
3/10/93	mibefradil	IND 39,901	As requested graphs provided of the decrease in diastolic blood pressure and change in PQ interval Vs plasma concentration of Ro 40-5967 as presented at the 1/29/93 End of Phase II Meeting.
3/16/93	mibefradil	IND 39,901	Information Amendment: Submitted a summary of the toxicologic and hemodynamic findings of the rat 6 and 12 month toxicology studies. Also, a summary of the rationale for the selection of dose in the 78-week mouse.
3/19/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol ROPR0008.
3/26/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol ROPR0008.
4/5/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol ROPR0008.
5/18/93	mibefradil	IND 39,901	Response to questions raised in 9/23/92 FDA letter to Marion Merrell Inc. concerning the manufacturing and controls section of IND 39,901 submitted

			6/24/92.
6/2/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol ROPR0008 and EC14484. Deleted Investigator, and Change of Address for investigator- Protocol ROPR0008.
8/2/93	mibefradil	IND 39,901	Protocol Amendment: New Investigator Protocol EC14484, and New Medical/Safety Monitor.
8/11/93	mibefradil	IND 39,901	Protocol Amendment: New Investigator Protocol EC14484.
8/16/93	mibefradil	IND 39,901	Annual Report
8/24/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol EC14484
9/8/93	mibefradil	IND 39,901	Protocol Amendment: New Protocol NC14509. In response to FDA's 12/4/92 letter to Marion Merrell Dow Inc., in which the Agency imposed a clinical hold on Protocol ROPR0004, submitted revised Protocol NC14509 for expedited review.
9/9/93	mibefradil	IND 39,901	Confirmed meeting to be held 10/1/93, and provided background material for Protocols BC14445 and NC14509A.
9/13/93	mibefradil	IND 39,901	Confirmed 9/30/93 meeting with FDA to discuss key issues regarding the planning and submission of a CANDA for Ro 40-5967.
9/24/93	mibefradil	IND 39,901	Protocol Amendment: New Protocol NC 14487A, New Investigators. Information Amendment: CMC.
9/27/93	mibefradil	IND 39,901	Protocol Amendment: New Protocol NC14646A, and New Investigators. New Medical Monitors. Also added contract research organization.
10/11/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14487A.
10/13/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NC14646A.
10/15/93	mibefradil	IND 39,901	Protocol Amendment: New Protocol NC14509, and New Investigator. Information Amendment: CMC - New Dosage Form, 25 mg tablet.
10/25/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol EC14484, and Protocol NC14646A.
10/26/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol NC14487A.
11/9/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NC14646A, Protocol NC14509A, and Protocol EC14484. Change of address under Protocol NC14646A.
11/11/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NC14487A, Addition of Subinvestigator; Investigator Change of Address.
11/30/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators under Protocol NC14646A, and Protocol EC14484.
12/3/93	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14487A.
1/4/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NC14509A, and NC14646A.
1/28/94	mibefradil	IND 39,901	Confirmation of meeting with FDA on 2/10/94 to discuss proposed clinical development plan for supporting a claim for the use of Ro 40-5967 in the treatment of congestive heart failure. Provided Protocols BC 14808, BC 14809 and BC14810.
2/1/94	mibefradil	IND 39,901	Protocol Amendment: New Investigator, Protocol NC14487A.

2/1/94	mibefradil	IND 39,901	Due to the receipt of additional information, pages 1 and 2 of Appendix 3 in Pre-Meeting submission Serial Submission No. 043 dated 1/28/94 have been revised. (This copy was submitted to the Consumer Safety Officer).
2/1/94	mibefradil	IND 39,901	Revised volume for Serial Submission No. 043. Due to the receipt of additional information, pages 1 and 2 of Appendix 3 in Pre-Meeting submission 043 dated 1/28/94 have been revised. Therefore, resubmitting submission.
2/4/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NC14646A, Protocol NC14509A, and Protocol EC14484.
2/23/94	mibefradil	IND 39,901	Initial Safety Report Protocol - ADE NC14487A.
3/2/94	mibefradil	IND 39,901	Follow-up Safety Report - ADE
3/8/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol NC14509A and Protocol NC14646A.
3/10/94	mibefradil	IND 39,901	Protocol Amendment: New Investigator for Protocol NC14487A, Addition of sub-investigator.
3/11/94	mibefradil	IND 39,901	Provided corrected Form FDA 1571 submitted with S-047 dated 2/23/94. It was noted that the medical monitor on this form was incorrect.
3/17/94	mibefradil	IND 39,901	Information Amendment: Toxicology.
3/22/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Reports
3/28/94	mibefradil	IND 39,901	IND Safety Report - Initial Written Report, ADE- Protocol - NC14646A.
3/29/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Reports.
3/31/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14509A, and NC14646A. Change of Address- Protocol NC14646A.
4/8/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Reports
4/27/94	mibefradil	IND 39,901	Protocol Amendment: Addition of Subinvestigator, and Change of Address, Protocol NC14487A.
5/12/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14509A.
5/24/94	mibefradil	IND 39,901	Safety Report: Report from a 104 week rat carcinogenicity study of preliminary findings. Meeting to be held on 6/7/94.
6/17/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14646A. Change of Address. Addition of Medical Monitor.
7/12/94	mibefradil	IND 39,901	Information Amendment: Pharmacology; Clinical - Research Reports.
7/15/94	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14509A, and Protocol NC14646A.
7/26/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Reports
7/29/94	mibefradil	IND 39,901	IND Safety Report: Initial Written Report - ADE Protocol - BC14443C.
8/12/94	mibefradil	IND 39,901	Protocol Amendment: Change in Protocol EC14484A: New Investigators NC14509A and NC14646A; Addition of Subinvestigators; Investigator Change of Address/Additional Research Facilities.
8/18/94	mibefradil	IND 39,901	Annual Report covering period of 6/2/93 through 6/1/94.

8/29/94	mibefradil	IND 39,901	Information Amendment: Clinical - Research Report
9/8/94	mibefradil	IND 39,901	Protocol Amendment: Addition of Subinvestigator Protocol NC14487A.
9/28/94	mibefradil	IND 39,901	Protocol Amendment: New Investigator, Protocol NC14646A; Addition of Subinvestigator; Investigator Change of Address; Addition of Research Facilities.
10/19/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Provided additional information as follow-up to 6/7/94 meeting with FDA.
10/20/94	mibefradil	IND 39,901	Information Amendment: CMC - Submitted specifications and directions for testing Ro 40-5967 50 mg film-coated tablets revised to provide the addition of a break bar to the tablet description.
11/3/94	mibefradil	IND 39,901	Confirmation of CANDA Meeting on 11/17/94 to discuss the design, format and operating systems to be used in the CANDA to be submitted with NDA for Posicor.
11/8/94	mibefradil	IND 39,901	Protocol Amendment: New Investigator Protocol NC14509A. Addition of Subinvestigators; Investigator Change of Address.
11/28/94	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Report
1/16/95	mibefradil	IND 39,901	Information Amendment: Clinical - Research Report.
2/1/95	mibefradil	IND 39,901	Protocol Amendment: Addition of Subinvestigators, Protocol NC14509A and NC14487A. Also Change of Address, Protocol NC14487A.
2/6/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol BK14541B, Information Amendment: CMC
2/8/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol NC14983A and New Investigators. Information Amendment: CMC.
2/24/95	mibefradil	IND 39,901	Information Amendment: Clinical - Research Report.
3/6/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol NC14983A.
3/10/95	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Report.
4/5/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14983A. Information Amendment: Toxicology - Research Report.
5/3/95	mibefradil	IND 39,901	Confirmed Pre-NDA Clinical Meeting to be held on 5/18/95 with FDA to discuss the preparation and format of the pre-clinical and clinical sections of NDA for Posicor.
5/8/95	mibefradil	IND 39,901	Protocol Amendment: New Investigator, Protocol NC14983A. Information Amendment: Toxicology - Research Report.
6/21/95	mibefradil	IND 39,901	Information Amendment: Toxicology - Research Reports
6/27/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol - NR14969B, New Investigator. Addition of Medical Monitors and Safety Evaluators. Information Amendment: CMC.
7/18/95	mibefradil	IND 39,901	IND Safety Report - Initial Written Report, ADE: Protocol: BC14444.
7/25/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NR14969B.
8/11/95	mibefradil	IND 39,901	Annual Report for period of 6/2/94 to 6/1/95.
8/16/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NR14969B.
9/11/95	mibefradil	IND	Protocol Amendment: New Protocol NC14975A and New Investigators.

		39,901	Information Amendment: CMC.
9/29/95	mibefradil	IND 39,901	Information Amendment: Pharmacology/Toxicology - Research Reports
10/2/95	mibefradil	IND 39,901	Information Amendment: Toxicology, Research Report.
10/12/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol (NR14967B) and New Investigators. Information Amendment: CMC.
10/16/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocol NC14983A, Protocol NC14975A, and Protocol NR14969B.
11/3/95	mibefradil	IND 39,901	Confirmed Pre-NDA Chemistry, Manufacturing and Controls Meeting on 11/16/95 to discuss the preparation of the CMC Section of NDA for Posicor.
11/3/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol (NR14966A) and New Investigators, Also transfer of obligations to contract research organization for Protocol NR14966A. Information Amendment: CMC.
11/9/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol NR14969B, Protocol NR14967B, and Protocol NC14983A.
12/12/95	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NR14966A, and NR14967B. Information Amendment: Preclinical toxicology research reports.
12/15/95	mibefradil	IND 39,901	Protocol Amendment: New Protocol and New Investigators for Protocol BC14447E. Information Amendment: CMC.
1/8/96	mibefradil	IND 39,901	Information Amendment - preclinical toxicology research reports
1/12/96	mibefradil	IND 39,901	Confirmation of 1/30/96 meeting with FDA to discuss data requirements for supporting drug superiority claims and the wording to be included in the Posicor package insert.
1/17/96	mibefradil	IND 39,901	Protocol Amendment -New Investigators, Protocol PR14966A, Protocol BC1 14447E and Protocol NR14967B. Also modified Form FDA 1572 previously submitted 10/16/95 (096) change in IRB address and 7/25/95(089) addition of sub-investigators and deletion of subinvestigator.
1/29/96	mibefradil	IND 39,901	Protocol Amendment - New Protocol NR15195A, Transfer of obligations to contract research organization for Protocol NR15195A. New Investigators for Protocol NR15195A. Information Amendment - CMC for Protocol NR15195A.
2/19/96	mibefradil	IND 39,901	Protocol Amendment - New Investigators Protocol NR15195A, BC14447E, and NR14966A. Change in Principal Investigator for Protocol NR14966A. Information Amendment.
3/13/96	mibefradil	IND 39,901	Protocol Amendment - New Investigators, Protocol NR15195A and Protocol BC14447E. Modifications to Forms 1572 for a couple of Investigators.
3/18/96	mibefradil	IND 39,901	Protocol Amendment - Change in Protocol NR15195A to NR15195B.
4/17/96	mibefradil	IND 39,901	Protocol Amendment - New Investigator, for Protocol NR15195B and for Protocol NR14966A.
6/4/96	mibefradil	IND 39,901	Protocol Amendment: New Investigators, Protocols NR14966A, BC14447E and NR14967B. Modifications to Forms FDA 1572 previously submitted for some Investigators.
8/12/96	mibefradil	IND 39,901	Protocol Amendment: New Investigators/Protocol NR15195B - Modifications to Forms FDA 1572 previously submitted.
8/16/96	mibefradil	IND 39,901	Protocol Amendment: New Protocol/New Investigator - Compassionate Use Treatment Protocol.
9/4/96	mibefradil	IND 39,901	Annual Report covering the period of 6/2/95 through 6/2/96.
9/13/96	mibefradil	IND 39,901	Protocol Amendment: New Investigators/Protocol BC14447E. Additional Investigator Information: Modifications to Forms FDA 1572 previously submitted.

10/16/96	mibefradil	IND 39,901	Protocol Amendment: New Investigators/Protocol NR15195B and Protocol NR14967B.
10/18/96	mibefradil	IND 39,901	Protocol Amendment - New Investigator, Study OM 074-002 and New Investigators. Information Amendment - CMC.
11/6/96	mibefradil	IND 39,901	Protocol Amendment: New Investigators/Protocol OM 074-002.
11/7/96	mibefradil	IND 39,901	Protocol Amendment - New Protocol NR15333A, New Investigator. Information Amendment - CMC.
1/6/97	mibefradil	IND 39,901	Protocol Amendment: Change in Protocol OM 074-002 - New Investigators - Protocol OM 074-002
1/15/97	mibefradil	IND 39,901	Clinical site audit. Protocol NR14966.
1/24/97	mibefradil	IND 39,901	Protocol Amendment: Compassionate Use Treatment Protocol - New Investigator.
1/24/97	mibefradil	IND 39,901	Protocol Amendment - New Protocol NR15486/M-30080 and New Investigator. Clinical and safety monitoring for Protocol NR15486/M-30080 will be transferred. Information Amendment - CMC.
1/31/97	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NR15333A and Protocol NR15195.
3/10/97	mibefradil	IND 39,901	Protocol Amendment: Change in Protocols - NR15195B to NR15195C, NR14967B to NR14967C, BC14447E to BC14447F.
3/10/97	mibefradil	IND 39,901	Protocol Amendment: New Investigators for Protocol NR15333A.
3/25/97	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NR15333A.
4/1/97	mibefradil	IND 39,901	Protocol Amendment: New Protocol/New Investigators/Transfer of Obligations to Contract Research Organization-Protocol NR15435A. Information Amendment: Chemistry, Manufacturing and Controls - Verapamil SR 240 mg Capsules and Placebo Capsules.
4/14/97	mibefradil	IND 39,901	Protocol Amendment: Compassionate Use Treatment Protocol - New Investigator.
5/1/97	mibefradil	IND 39,901	Protocol Amendment: New Investigators - Protocol NR15333A and Protocol NR15435A.
6/11/97	mibefradil	IND 39,901	Protocol Amendment - New Investigators - Protocol NR15435A and Protocol NR15333A.

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Posicor NDA 20,689

Filing Date	Name	Type/ Number	Description
3/8/96	POSICOR	NDA 20-689	Posicor Oral for treatment of hypertension and chronic stable angina pectoris.
3/8/96	POSICOR	NDA 20-689	Provided ten copies of the summary of Posicor NDA Clinical Studies for use at NDA Review Planning Meeting.
3/18/96	POSICOR	NDA 20-689	Provided two diskettes containing ASCII data sets for the two carcinogenicity studies submitted in NDA.
3/19/96	POSICOR	NDA 20-689	Schedule training session for FDA reviewers on the use of the Posicor CANDA.
3/21/96	POSICOR	NDA 20-689	Response to FDA's request of 2/13/96, submitted documentation specified in "Items to Request From Sponsor to Assist Bioresearch Monitoring Audits" as an aid in planning audits of the pivotal clinical studies in the Posicor NDA.
4/11/96	POSICOR	NDA 20-689	As a follow-up to our CANDA training meeting, submitted copies of the "Mibefradil CANDA - Release Notes" to be distributed to the reviewers.
4/16/96	POSICOR	NDA 20-689	As requested in FDA's 3/22/96 FAX submitted two Toxicology Reports.
4/22/96	POSICOR	NDA 20-689	As requested, submitted additional information concerning the Posicor CANDA.
4/22/96	POSICOR	NDA 20-689	As requested, provided a table of mean PQ intervals at baseline, 2 hours and 4 hours following administration of mibefradil or placebo in studies P5082 and EC14605.
4/29/96	POSICOR	NDA 20-689	Provided copies of the Mibefradil CANDA Release Notes 1.0a to be distributed to reviewers using the Posicor CANDA.
4/30/96	POSICOR	NDA 20-689	As requested, submitted for all adverse event presentations in the Posicor NDA which presented AEs excluding events unrelated to therapy the corresponding presentation for all adverse events regardless of relationship to test drug.
5/16/96	POSICOR	NDA 20-689	Response to request and as discussed at the teleconference of 5/13/96, submitted data files, control files and outputs of the population PK-PD analysis using NONMEN on diskette.
5/17/96	POSICOR	NDA 20-689	Response to request, submitted in Appendix A documentation for Study K13003 and Appendix B, a listing of investigators who participated in more than one of the pivotal studies.
5/21/96	POSICOR	NDA 20-689	Response to inquiry concerning one subject in study BD14111.
5/30/96	POSICOR	NDA 20-689	Response to request, submitted corrected QT evaluations, and heart rhythm strip for a Patient.

*Not all communications from FDA to Roche listed in this Exhibit 7.

5/30/96	POSICOR	NDA 20-689	Response to FDA request, submitted listings of patient nitroglycerin consumption for investigational sites 12980, 12981, 12984 and 13110 for study BC14047.
5/31/96	POSICOR	NDA 20-689	Response to FDA's request on 5/14/96 for clinical efficacy data for study protocols K13000, BC14047, NC14509, BC14446, EC14484 and BC14444.
6/11/96	POSICOR	NDA 20-689	Response to request of 6/3/96, provided copies of toxicology final study reports and WP 5.1 Disks for Integrated Preclinical Summary - Pharmacology and Toxicology Sections.
6/18/96	POSICOR	NDA 20-689	Response to request for clinical data: Graphical presentations of mean changes in QTc interval for Study P5192 and concentration-effect data from Day 1 in Study P5094.
6/18/96	POSICOR	NDA 20-689	Response to FDA letter dated 5/23/96 concerning the Chemistry, Manufacturing and Controls Sections of the Posicor NDA.
6/18/96	POSICOR	NDA 20-689	Response to request for human pharmacokinetic data. Submitted the following: Individual Concentration/Effect Data, Study P5094 and Validation Data, Study BD14111.
6/19/96	POSICOR	NDA 20-689	Response to request for clinical data. Provided the following information: Heart Rate and Sitting Systolic Blood Pressure by Dose, Baseline ETT Measurements, Source of Percentages given in Section 2, Volume 3, page 229, and Dosage Recommendations.
6/20/96	POSICOR	NDA 20-689	Response to request - Clinical Audit Information.
7/10/96	POSICOR	NDA 20-689	Four Month Safety Update
7/12/96	POSICOR	NDA 20-689	Response to request, submitted two tables which provide the values for heart rate, QT and QTc at trough for verapamil and mibefradil in study P5183.
7/24/96	POSICOR	NDA 20-689	Submitted background information concerning the effect of Posicor on QT intervals in preparation for the meeting with FDA on 7/30/96.
8/6/96	POSICOR	NDA 20-689	Amendment - Toxicology Final Study Report
8/7/96	POSICOR	NDA 20-689	Provided information regarding Study BC14443.
8/8/96	POSICOR	NDA 20-689	Response to request, submitted datasets for concentration-effect relationship and QTc measurements which were presented at the 7/30/96 meeting.
8/13/96	POSICOR	NDA 20-689	Response to request, submitted assay validation data for the following studies: Attachment 1: BD14494, Ro 40-5967 and Ro 40-5966 - Attachment 2: WK15071, Quinidine and 3-OH-quinidine.
8/13/96	POSICOR	NDA 20-689	Response to request for information, submitted documentation for Protocol BC14047 for the following study sites: 12981, 12943.
8/14/96	POSICOR	NDA 20-689	Response to FDA request for Information - Provided a copy of submissions dated 3/21/96 and 8/13/96 concerning study sites for Protocol BC14047: 12981, 12943.

8/21/96	POSICOR	NDA 20-689	Provided additional information subsequent to the submission dated 8/13/96.
8/23/96	POSICOR	NDA 20-689	Response to request for Information - Provided a letter RE: Protocol BC14047, (site 12981).
9/4/96	POSICOR	NDA 20-689	Response to FDA letter dated 8/15/96, provided samples to help facilitate the method validation studies. (Samples sent to Division of Drug Analysis-HFH-300, Drug Monitoring Branch, St. Louis, MO.)
9/4/96	POSICOR	NDA 20-689	Response to FDA letter dated 8/15/96, provided samples to help facilitate the method validation studies. (Samples sent to FDA, U.S. Customs House, Philadelphia, PA.)
9/11/96	POSICOR	NDA 20-689	Response to facsimile dated 9/10/96. Provided copies of the methods of analyses used for the release of the drug substance and drug product (50 and 100 mg).
9/12/96	POSICOR	NDA 20-689	Provided copies of pages from Research Report, as requested.
9/13/96	POSICOR	NDA 20-689	Pre-meeting submission in preparation for 9/20/96 meeting with FDA.
9/17/96	POSICOR	NDA 20-689	Response to request for information. Provided the following: Tables corresponding to marked laboratory abnormalities in placebo-controlled studies/hypertension and angina. Summaries of marked laboratory abnormalities.
10/7/96	POSICOR	NDA 20-689	Response to request. Submitted the following: Attachment I: Tables providing the combined incidence of adverse experiences coded. Attachment II.
10/10/96	POSICOR	NDA 20-689	Submitted the unaudited draft report for the in-life necropsy phases of the 104 Week Oral (Gavage Administration) Oncogenicity Study in the Rat, as agreed at the meeting on 5/29/96.
10/10/96	POSICOR	NDA 20-689	Response to FDA for information requested at 9/20/96 meeting. Provided ECGs for selected patients in studies EC14479 and ED14605.
10/15/96	POSICOR	NDA 20-689	Response to the 9/25/96 request for efficacy data for study EC14484. Provided the following: 1. Description of the analysis dataset used in the efficacy analysis 2. Diskette of dataset E14484L.SD2.
10/17/96	POSICOR	NDA 20-689	Pre-meeting submission in preparation for a meeting with FDA on 10/31/96 to discuss the effect of Posicor on electrocardiographic parameters. Provided a compilation of all data previously presented on the subject issue.
11/5/96	POSICOR	NDA 20-689	Response to request of 10/21/96. RE: steady state plasma levels, efficacy and ECG changes.
11/6/96	POSICOR	NDA 20-689	Pre-Meeting Submission was submitted 10/17/96 in preparation for 10/31/96 meeting to discuss the effect of Posicor on electrocardiographic parameters. Meeting of 11/12/96 is scheduled to discuss the agenda for the Advisory Board.

11/22/96	POSICOR	NDA 20-689	Response to request of 11/13/96. Provided a listing of patients with leukocyte count < 3 G/L and/or neutrophil count < 1.5 G/L.
11/26/96	POSICOR	NDA 20-689	Information Amendment - Final Study Report for the inlife and necropsy phases of the 104 Week Oral (Gavage Administration) Oncogenicity Study in the Rat. Additionally, we also submitted histopathological data on diskette.
11/26/96	POSICOR	NDA 20-689	Provided the ECGs requested at the meeting of 9/20/96.
11/26/96	POSICOR	NDA 20-689	Information Amendment: Clinical. Provided data sets on diskette of plasma concentrations of mibefradil and changes in QTc.
12/6/96	POSICOR	NDA 20-689	Amendment - CMC, response to FDA's letter of 5/23/96 citing reviewer questions concerning the CMC section of the Posicor NDA.
12/16/96	POSICOR	NDA 20-689	Information Amendment - (Pharmacology) Submitted synopses of study results for the interaction studies of Posicor with terfenadine or metoprolol.
1/21/97	POSICOR	NDA 20-689	Cardio-Renal Advisory Committee Briefing Document in preparation for the February 1997 meeting.
1/21/97	POSICOR	NDA 20-689	Amendment - Pharmacology, Clinical Information - Pre-meeting submission for 2/7/97 meeting with Division of Cardio-Renal Drug Products to review, prior to presentation at the Advisory Committee, new information concerning Posicor.
1/29/97	POSICOR	NDA 20-689	Provided electrocardiograms for certain patients.
1/31/97	POSICOR	NDA 20-689	Information Amendment: Toxicology - In preparation for meeting with the Carcinogenicity Assessment Committee on 2/11/97, submitted the following document: Posicor (mibefradil): Evaluation of the Oral Tumours in Rat Carcinogenicity Studies.
1/31/97	POSICOR	NDA 20-689	Information Amendment: Clinical - Pre-meeting submission for 2/7/97 meeting. Submitted background information.
2/13/97	POSICOR	NDA 20-689	Information Amendment: Clinical - Draft Final Study Report Study No. M30100.
2/13/97	POSICOR	NDA 20-689	In preparation for the 2/28/97 meeting of the Cardio-Renal Advisory Committee, provided the letter from the independent Safety Data Monitoring and Advisory Committee (ISDMAC) of the Mach 1 Trial.
3/10/97	POSICOR	NDA 20-689	Information Amendment: Clinical Pharmacology/Biopharmaceutics. Final study reports: Research. Protocol M30037 - Protocol BP15205, - Protocol BQ15196(M-30030).
3/13/97	POSICOR	NDA 20-689	Response to FDA's 2/14/97 request for additional laboratory historical control data in rats of the same strain as those used in the two-year diet admix carcinogenicity study with mibefradil
3/18/97	POSICOR	NDA 20-689	Information Amendment: Revised Draft Package Insert Incorporating FDA's Comments of 3/5/97.

3/27/97	POSICOR	NDA 20-689	Information Amendment: Chemistry, Manufacturing and Controls. Two minor modifications-Appendix I Modification of the Manufacturing Procedure for Posicor 50 mg and 100 mg Tablets.
4/15/97	POSICOR	NDA 20-689	Information Amendment: Clinical - Final Safety Summary incorporating all safety data which became available since 5/31/96, the clinical cut-off for the 4-Month Safety Update and 12/31/96, the clinical cut-off for the subject report.
4/22/97	POSICOR	NDA 20-689	Response to FDA request for information dated 12/16/96. Provided the following information: - Assay Validation Data for: i) mibefradil and metabolite (Protocol BD14494) ii) mibefradil (Protocol P5094) iii) 3-hydroxy quinidine (Protocol WK15071) iv) mibefradil (Protocol BD14401).
5/12/97	POSICOR	NDA 20-689	Launch Promotional Material - Provided for FDA review the Initial Press Release and Video News Release Script to be issued following the approval of Posicor. Current package insert (March 1997) and copies of the cited references are also provided.
6/13/97	POSICOR	NDA 20-689	Response to Approvable Letter of 6/11/97 - Draft Package Insert.
6/19/97	POSICOR	NDA 20-689	Draft Package Insert - Follow-up to teleconference of 6/18/97 and the Division of Cardio-Renal Drug Products.
6/19/97	POSICOR	NDA 20-689	Market Exclusivity Information for inclusion the NDA.

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#12

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,808,605 Attn: Box Patent Ext.

Inventors: Branca, et al.

Issue Date: February 28, 1989

For: TETRAHYDRONAPHTHALENE DERIVATIVES AS CALCIUM ANTAGONISTS

DECLARATION AND POWER OF ATTORNEY FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
August 5, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, George W. Johnston, a Vice President of Hoffmann-La Roche Inc. ("ROCHE"), which submits the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

(1) ROCHE is the owner of record of U.S. Patent No. 4,808,605 and I am authorized to obligate ROCHE;

(2) I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from ROCHE to act on its behalf in patent matters;

(3) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 4,808,605 pursuant to 35 U.S.C. § 156 and 37 C.F.R. §1.710 et seq;

(4) I believe this patent is subject to extension under 35 U.S.C. § 156 and 37 C.F.R. §1.710;

(5) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(6) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156, and more particularly, in 37 C.F.R. §1.720.

I hereby appoint the following attorneys as agents for ROCHE under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith: George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542), Patricia S. Rocha-Tramaloni (Reg. No. 31054), and Ellen Ciambrone Coletti (Reg. No. 34140).

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(973) 235-5171

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application or any extension of U.S. Patent No. 4,808,605.

Respectfully submitted,
HOFFMANN-LA ROCHE INC.
By: George W. Johnston
George W. Johnston
Vice President
Date: August 5, 1997

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